19 September 2019
EMA/CHMP/13746/2020
Committee for Medicinal Products for Human use (CHMP)

Withdrawal Assessment Report

Idhifa

International non-proprietary name: enasidenib

Procedure No. EMEA/H/C/004324/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of Contents

List of abbreviations **3**

1. CHMP Recommendation **6**

2. Executive summary **7**

2.1. Problem statement 7
2.2. About the product 10
2.3. The development programme and scientific advice 10
2.4. General comments on compliance with GMP, GLP, GCP 11
2.5. Type of application and other comments on the submitted dossier 12

3. Scientific overview and discussion **13**

3.1. Quality aspects 13
3.2. Non clinical aspects 17
3.3. Clinical aspects 27
3.4. Risk management plan 125
3.5. Pharmacovigilance system 132

4. Orphan medicinal products **132**

5. SAG oncology consultation **133**

6. Benefit risk assessment **136**

6.1. Therapeutic Context 136
6.2. Favourable effects 138
6.3. Uncertainties and limitations about favourable effects 138
6.4. Unfavourable effects 141
6.5. Uncertainties and limitations about unfavourable effects 141
6.6. Effects Table 142
6.7. Benefit-risk assessment and discussion 143
6.8. Conclusions 145

List of abbreviations

2-HG	2-hydroxyglutarate
ADR	Adverse drug reactions
AE	Adverse event
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AMLSG	ML Study Group
ANC	Absolute neutrophil count
API	Active pharmaceutical ingredient
AS	Active substance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-10	Area under the concentration-time curve from 0 to 10 hours
AUC0-24	Area under the concentration-time curve from 0 to 24 hours
BCRP	Breast cancer resistance protein
BID	Twice daily
BMT	Bone marrow transplant
BSC	Best supportive care
BUN	Blood urea nitrogen
(C)IPC	(Critical)In-process control
(C)PP	(Critical)Process parameter
C1D1	Cycle 1 Day 1
C_{max}	Maximum observed plasma concentration
CCR	Conventional care regimen
CDx	Companion diagnostic
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CML	Chronic myelogenous leukemia
CQA	Critical Quality Attribute
CR	Complete response; same as complete remission
CRi	Complete response with incomplete hematologic recovery based on neutrophils
CRp	Complete response with incomplete platelet recovery
CRR	Complete response rate
CSR	Clinical study report
CYP	Cytochrome
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOCR	Duration of complete response
DOR	Duration of response
DP	Drug product
DS	Design Space or Drug Substance
DSRC	Differentiation Syndrome Review Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	Event-free survival

ELN	European LeukemiaNet
EU	European Union
FDA	Food and Drug Administration
FT-IR	Fourier transform-Infrared
GC	Gas chromatography
Hgb	Hemoglobin
HMA	Hypomethylating agent
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
IC50	Inhibitory concentration in 50%
IDH,	IDH2 Isocitrate dehydrogenase, isoform 2
IRAC	Independent Response Adjudication Committee
ITT	Intent-to-treat
IV	Intravenous
IWG	International Working Group
KM	Kaplan-Meier
LDAC	Low dose cytarabine
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
mCR	Marrow complete response
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
mIDH2	mutant isocitrate dehydrogenase isoform 2
MLFS	Morphologic leukemia-free state
MOA	Mechanism of action
MTD	Maximum tolerated dose
NA	Not applicable/available/achievable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NIL	Non-infectious leucocytosis
NOAEL	No observed adverse effect level
OAT	Organic anion transporter
OCT	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
PETHEMA	Programa Espanol de Tratamientos en Hemtologia group
PD	Pharmacodynamic(s)/progressive disease
PK	Pharmacokinetic(s)
PR	Partial response; same as partial remission
PS	Performance status
PT	Preferred term
QD	Once daily
QoL	Quality of life
RBC	Red blood cell
RARECARE	Surveillance of Rare Cancers in Europe
RP2D	Recommended Phase 2 dose
R/R	Relapsed/refractory
SC	Subcutaneous

SCE	Summary of Clinical Efficacy
SD	Stable disease/standard deviation
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T_{max}	Time to maximum plasma concentration
TTBR	Time to best response
TTCR	Time to complete response
TTR	Time to response
UGT	Uridine diphosphate-glucuronosyltransferase
US	United States
VAF	Variant allele frequency
WBC	White blood cell
WHO	World Health Organization

1. CHMP Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Idhifa (enasidenib), an orphan medicinal product in the treatment of

- Initially proposed indication: "*adult patients with relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase 2 (IDH2) mutation*"
- Adapted to: *adult patients with intermediate or poor cytogenetic risk, relapsed or refractory AML with an isocitrate dehydrogenase 2 (IDH2) mutation who are ineligible for intensive treatment and*
    - *Have previously failed low intensity treatment, or*
    - *Have primary refractory disease or relapsed after having failed previous intensive treatment including haematopoetic stem cell transplantation.*

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues (Section 8).

Questions to be posed to additional experts

SAG Oncology was consulted with regard to the relevance of the enasidenib data to support an indication in R/R AML with an IDH2 mutation (please refer to section 5, SAG Oncology consultation).

Inspection issues

GMP inspection(s)

No GMP inspections are deemed necessary at this stage within the scope of this MAA evaluation procedure.

GCP inspection(s)

FDA performed the following GCP inspections for study AG221-C-001:

- Sponsor inspection:
    - Celgene Corp, Summit, NJ, USA) (13, 15-17 March 2017)
- Site inspections for the following sites:
    - Stanford Cancer Center, Stanford, CA, USA (11-29 April 2016)
    - Memorial Sloan-Kettering Cancer Center, New York, NY, USA (13-16 March 2017)
    - Institut Gustave Roussy – Service DITEP, Villejuif, France (24-27 April 2017)
    - University of Texas MD Anderson Cancer Center, Houston, TX, USA (2-5 May 2017)

By FDA no finding was judged as having a potential impact on data quality and /or patients' rights and wellbeing.

EMA performed the following routine GCP inspections for study AG221-C-001 (GCP/2018/023):

- CRO:
- Site inspection:
    - Institut Gustave Roussy – Service DITEP, Villejuif, France (05-09 Nov 2018)

As critical and major findings were observed during the inspections, full GCP compliance could not be attested for the trial conduct. However, the quality of the data reported in the interim study report of trial AG221-C-001 is considered sufficient for their use in this marketing authorisation application.

New active substance status

Based on the review of the data the CHMP considers that the active substance enasidenib contained in the medicinal product Idhifa is to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The claimed therapeutic indication is:

- Initially proposed indication: "*Treatment of adult patients with relapsed or refractory acute myeloid leukaemia (R/R AML) with an isocitrate dehydrogenase 2 (IDH2) mutation*"
- Adapted to: *adult patients with intermediate or poor cytogenetic risk, relapsed or refractory AML with an isocitrate dehydrogenase 2 (IDH2) mutation who are ineligible for intensive treatment and*
    - *Have previously failed low intensity treatment, or*
    - *Have primary refractory disease or relapsed after having failed previous intensive treatment including haematopoetic stem cell transplantation.*

As to the study protocol (Amendment 7) of the pivotal phase 1/2 study AG221-C-001 the following definitions applied:

- Diagnosis of AML had to be performed according to WHO criteria (Swerdlow et al 2008).
- 'Relapsed' AML (defined only for subjects who have previously attained CR, CRi, CRp or MLFS) is defined as "bone marrow blasts ≥5 percent; or reappearance of blasts in the blood; or development of extramedullary disease)".
- 'Refractory' (resistant) AML is defined as "failure to achieve CR or CRi (general practice; Phase 2/3 trials), or failure to achieve CR, CRi or PR (Phase 1 trials); only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukaemia by blood and/or bone marrow examination".

Details of the definition of a positive IDH2 status which have been applied and which should be considered treatment relevant lack clarification (OC).

2.1.2. Epidemiology

AML is a rare disease. The annual crude incidence of AML is 3.7 per 100,000 and the number of new cases per year in Europe is estimated at 18,400. AML is the most frequent form of leukaemia, accounting for approximately 25% of all leukaemias in adults in the Western world. The incidence of AML increases sharply with age, ranging from 1.8 cases per 100,000 people aged less than 65 years of age to 13.7 cases per 100,000 people over 65 years of age. More than half of the subjects with newly diagnosed

AML in developed countries are over 65 years of age, with a median age at diagnosis of 67, and AML is more common in men than in women. The estimated prevalence of AML in the European Union (EU) is 1.1 per 10,000.

2.1.3. Biologic features

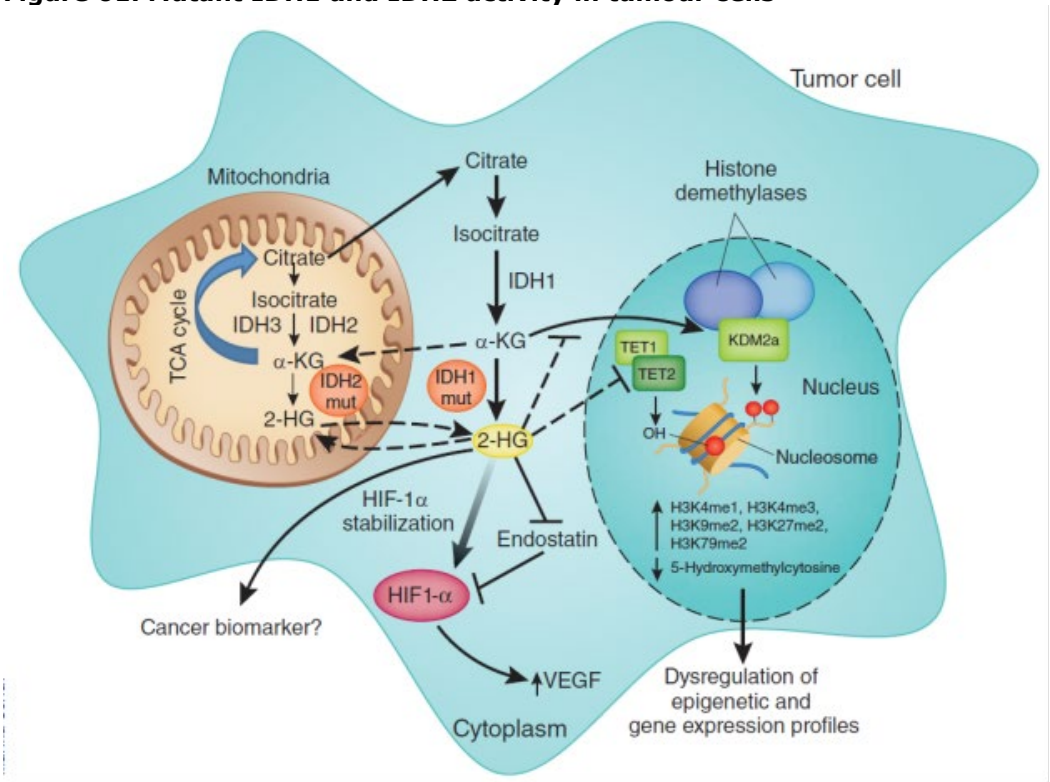
Acute myeloid leukaemia

Acute myeloid leukaemia is a form of leukaemia – i.e. cancer of the white blood cells – characterised by infiltration of proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated haematopoietic cells of myeloid lineage in the bone marrow, blood, and other tissues. The prognosis of patients with AML varies dramatically as a result of a number of factors, including age, performance status, and cytogenetic and/or molecular genetic alterations (list incomplete).

IDH2 mutation

Isocitrate dehydrogenase protein (IDH) is a critical metabolic enzyme in the citric acid cycle catabolising the oxidative decarboxylation of isocitrate to produce CO2 and α-ketoglutarate (α-KG). IDH1 is localised both in peroxisomes and cytoplasm, IDH2 is the mitochondrial isoform. The mutant IDH enzymes (mutant IDH1 and IDH2; no mutations have been described in IDH3) possess a novel enzymatic activity, catalysing the reduction of α-KG to the D-enantiomer of 2-hydroxyglutarate (D-2-HG, also known as R(-)2-HG) leading to D-2-HG accumulation (no intermediate product in citric acid cycle). D-2-HG induces epigenetic dysregulation and a block of haematopoietic cell differentiation that increases immature precursors and progenitor cells at the expense of mature cells.

Figure 01. Mutant IDH1 and IDH2 activity in tumour cells



Source: Prensner and Chinnaiyan 2011 (Nature Medicine 17, 291–293 (2011); doi:10.1038/nm0311-291)

2.1.4. Clinical presentation, diagnosis and prognosis

In AML, leukaemic blasts replace normal blood cells in bone marrow and peripheral blood, which leads to anaemia, neutropenia, and thrombocytopenia. This is associated with symptoms of fatigue, shortness of breath, disturbed wound healing, infections and bleedings. If left untreated, AML results in death within a few weeks to months.
The procedures used to diagnose and classify AML are: morphologic assessment of bone marrow specimens and blood smears (with ≥20% blasts in the bone marrow or peripheral blood being diagnostic of AML), analysis of the expression of cell-surface and cytoplasmic markers (by flow cytometry), identification of chromosomal findings (through cytogenetic testing), and screening for selected molecular genetic alterations. Currently, the following molecular markers are used as part of standard clinical practice for risk stratification (European LeukemiaNet recommendations; (Dohner et al., 2017)): Fms-like tyrosine kinase 3 (FLT3), nucleophosmin-1 (NPM1), CCAAT/enhancer-binding protein alpha (CEBPA), RUNX1, TP53 and ASXL1. This list will likely be expanded in the future.

Prognostic factors in AML can be subdivided into those that are related to the patient and those that are related to the disease. Patient-associated factors (e.g., increasing age, coexisting conditions, and poor performance status) commonly predict treatment-related early death, whereas disease-related factors (e.g., white-cell count, prior myelodysplastic syndrome or cytotoxic therapy for another disorder, and leukaemic-cell genetic changes) predict resistance to current standard therapy.

In this application, the claimed indication concerns patients with R/R AML who have IDH2 mutated disease. Details of the definition of a positive IDH2 status lack clarification (OC). The frequency of reported IDH2 mutations in AML is between 8.2% and 19.3%, with a weighted average of 11.2%. In subjects with IDH2 mutated AML, the R140 mutation is the more common and represents approximately 70% of the cases, while the R172 mutation represents approximately 30%.

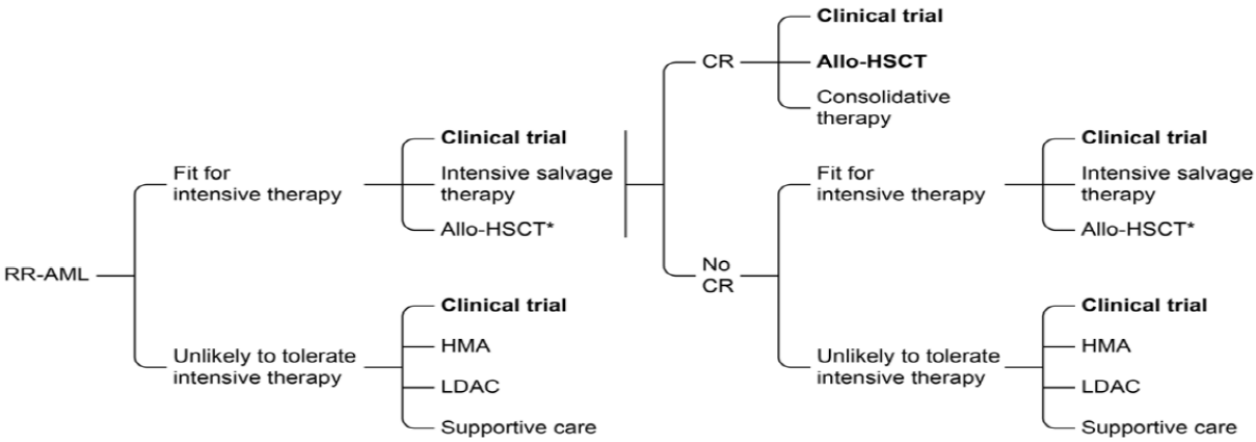
Altogether, survival for R/R AML differs significantly due to the large heterogeneity of this target population; a literature review showed a median survival in the range of 2 to 13 months. The prognostic impact of mutated IDH2 in AML remains controversial. As to Medeiros 2017 several studies have suggested an association with adverse outcomes whereas others have failed to identify any clear influence on clinical response or survival and still others report improved survival. Differences in prognostic findings may reflect variations in study methodologies; also the mutational context may influence AML prognosis. Currently it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH2 in AML and further confirmation in prospective studies is needed to more clearly elucidate the effect.

2.1.5. Management

As stated the R/R AML population is very heterogeneous with diverse prognoses. The only curative treatment option in R/R AML is HSCT (mostly after intensive chemotherapy). However, intensive chemotherapy and HSCT are associated with a significant treatment-related morbidity and mortality. Therefore, the overarching question in the treatment of R/R AML for every patient is to decide on the eligibility for intensive therapy; and the most important trade-off in each patient is to weigh the higher treatment-related morbidity and mortality and the long duration of hospitalisation that is associated with intensive chemotherapy regimens and HSCT against the possibility to be cured. Several intensive chemotherapy treatment options are commonly used, including intensive re-induction (with an anthracycline, anthracenedione and/or cytarabine) or purine analogue-containing (eg, fludarabine, cladribine, clofarabine) salvage chemotherapy; but there is no intensive treatment regimen that is clearly

more beneficial than another. Non-curative treatment options include hypomethylating agents (HMA), low-dose cytarabine (LDAC) or supportive care. In consequence, treatment in the R/R AML setting should be individualized and will depend on whether treatment with a curative intent is realistically possible and whether the patient can tolerate or wishes to undergo such treatment. A general treatment algorithm is provided in the figure below.

Figure 02. Treatment algorithm for R/R AML



Source: Ramos, 2015

While some drugs are approved in the EU for the treatment of adult patients with newly diagnosed AML (e.g. Dacogen®, Vidaza®, Rydapt®, Mylotarg®), no drug is explicitly approved in the EU for the use in R/R AML yet.

2.2. About the product

Enasidenib (AG-221, CC-90007) is an orally administered first-in-class, selective inhibitor of mutant IDH2 enzyme with activity against both R140 and R172 variants promoting the differentiation of leukemic cells into normalised mature cells.

The Applicant claims therapeutic indication for: "*Treatment of adult patients with relapsed or refractory acute myeloid leukaemia (R/R AML) with an isocitrate dehydrogenase 2 (IDH2) mutation", and recommends a dose of enasidenib of "100 mg to be taken orally once daily until disease progression or unacceptable toxicity". "Treatment for patients without disease progression or unacceptable toxicity is recommended for a minimum of 6 months to allow time for clinical response*".

2.3. The development programme and scientific advice

Clinical development program
The clinical development program for enasidenib includes 10 completed or ongoing studies, and 1 planned study (as of 01 Sep 2017).
Of these 10 studies, 4 are clinical pharmacology studies to assess the PK profile, bioavailability, and the effect of food on the PK of enasidenib in healthy volunteers (all completed); and the PK profile in subjects with moderate or severe hepatic impairment (ongoing). The planned study will evaluate drug-drug interactions in subjects with AML and an IDH2 mutation who have failed one line of therapy or declined

standard of care. The other 5 studies are phase 1 to 3 studies evaluating safety and efficacy in subjects with advanced haematologic malignancies.
The efficacy claims of enasidenib in IDH2 mutant R/R AML patients are based on a single pivotal uncontrolled phase 1/2 study, namely study AG221-C-001.

To assess the benefit and value of enasidenib in the context of existing therapies used in the R/R AML population, the Applicant performed

- a systematic review of published literature and
- a comparison of the AG221-C-001 data versus AML registry data collected in R/R AML patients with an IDH2 mutation treated with conventional treatments in a real-world setting (the mentioned registries being the AMLSG (Germany) and PETHEMA (Spain)).
- A propensity score matching analysis of study AG221-C-001 vs French Chart Review and vs AMLSG

To further support these results in the proposed indication in the scope of a CMA application, the Applicant proposes confirmation of benefit-risk (overall survival) as a post-authorisation measure with submission of the clinical study report from the ongoing open-label randomised controlled phase 3 study AG-221-AML-004 (IDHENTIFY) comparing enasidenib monotherapy with conventional care regimens in an elderly (≥60 years) late stage (2nd and 3rd relapse) IDH2 mutated R/R AML population (primary endpoint: OS).

Scientific advice
The applicant received feedback for pivotal phase 1/2 study AG221-C-001 in 4 national scientific advice procedures between June and September 2017 (AEMPS, DMA, BfArM and MPA) on the proposed clinical data package as basis for an MAA in R/R AML. Of note, study AG221-C-001 was already fully recruited at that time and agency feedback was given shortly before data cut-off (data cut-off for presented CSRs in this MAA 01 Sep 2017). Therefore, no questions on the study design could be discussed.
Furthermore, the applicant obtained CHMP feedback in the planning process of study AG-221-AML-004 on the study design in 2015 (EMEA/H/SA/3052/1/2015/III). Of note, at that time study AG-221-AML-004 was discussed as pivotal study for a full MA in an indication according to the study population. As to the information presented, the relevant issues of the advice were implemented.

Paediatric investigation plan (PIP)
A PIP has been agreed with the EMA / PDCO in October 2017 (P/0293/2017). The indication targeted by the PIP is "treatment of patients from 2 to less than 18 years of age with IDH2-mutated acute myeloid leukaemia". A waiver was granted for the paediatric population from birth to less than 2 years of age. The development of an age-appropriate formulation is planned. Two clinical studies are planned to be performed in paediatric populations:

- Study 2: Multicentre, single-arm, open label study to evaluate the safety, antitumour activity, and PK of enasidenib in R/R AML paediatric patients with IDH2 mutation (after at least 2 induction attempts) from 2 to less than 18 years of age (and adults).
- Study 3: Multicentre, open label study to evaluate efficacy and safety of enasidenib in combination with standard of care anti-cancer therapy in AML paediatric patients with IDH2 mutation from 2 to less than 18 years of age (and adults).

Date of completion of the PIP is by June 2026.

2.4. General comments on compliance with GMP, GLP, GCP

No GMP inspections are deemed necessary at this stage within the scope of this MAA evaluation procedure.

GLP
The safety pharmacology and pivotal toxicology studies were performed in accordance with Good Laboratory Practices (GLP).

GCP
The Applicant assures that all clinical studies in the enasidenib MAA, including the AG221-C-001 study, were conducted according to GCP guidelines with the ethical principles that have their origins in the Declaration of Helsinki and following ICH guidelines.

For further information of the performed FDA und EMA inspections of trial AG221-C-001 please refer to section 1 "GCP inspections" above.

2.5. Type of application and other comments on the submitted dossier

Legal basis
This application concerns a centralised procedure under 'mandatory scope' [Article 3(1) of Regulation (EC) No 726/2004; Annex (3) - New active substance for mandatory indications].

The legal basis for this application refers to article 8 (3) of Directive 2001/83/EC as amended. Idhifa contains a new active substance.

Accelerated procedure
NA

Conditional approval
According to Article 14(7) of regulation (EC) No 726/2004 and commission regulation (EC) No 507/2006 has applied for a conditional marketing authorization.

In order to confirm the efficacy and safety of enasidenib and the benefit-risk in the proposed indication, Celgene proposes to provide the study report on the primary endpoint of OS of the ongoing randomised controlled study AG-221-AML-004: "A Phase 3, multicentre, open-label randomised study comparing the efficacy and safety of AG-221 (CC-90007) versus conventional care regimens in older subjects with late stage acute myeloid leukaemia harbouring an isocitrate dehydrogenase 2 mutation (the "IDHENTIFY" trial)". The study is currently running worldwide and includes 9 countries in the EEA.

AML is a life-threatening disease.

Enasidenib was designated an orphan medicinal product in the EU for the treatment of AML on 28 Apr 2016 (EU/3/16/1640). The application for orphan drug designation was based on the criterion of significant benefit over existing methods of treatment for the condition."

Exceptional circumstances
NA

1-year data exclusivity
NA

Significance of paediatric studies
NA

New active substance status

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that enasidenib is to be qualified as a new active substance.

Orphan designation
Enasidenib was designated as an orphan medicinal product EU/3/16/1640 on 28.04.2016 in the following condition: Treatment of acute myeloid leukaemia.

Similarity with orphan medicinal products
The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products. Assessment of these claims is appended.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The present Marketing Authorisation Application concerns a centralised procedure submitted by Celgene Europe Ltd in accordance with Article 3(1) – Annex (4) Orphan Designation (enasidenib was granted EU Orphan designation for the treatment of AML on 28 April 2016 (EU/3/16/1640).

The concerned medicinal product is Idhifa (enasidenib) 50 mg and 100 mg film coated tablets.

Full information is provided in the application with respect to the active substance enasidenib mesilate. No ASMF or CEP is present.

3.1.2. Active Substance

General Information

Enasidenib (AG-221, CC-90007) is a mesylate salt of a weak base. The drug substance active moiety and the methanesulfonic counter ion are at a 1:1 ratio. Information on description, melting point, chiral/stereochemistry, solubility, solution pH, pKa, partition coefficients, UV-visible characteristics, hygroscopicity, mesylate salt and polymorphism is provided.

Manufacture, process controls and characterisation

Enasidenib (AG-221, CC-90007) is a mesylate salt of a weak base. The drug substance active moiety and the methanesulfonic counter ion are at a 1:1 ratio. Information on description, melting point, chiral/stereochemistry, solubility, solution pH, pKa, partition coefficients, UV-visible characteristics, hygroscopicity, mesylate salt and polymorphism is provided.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The drug substance specifications include the following controls: Appearance, Identification FT-IR, Identification HPLC, Solid Form (XRPD), Assay (HPLC), Related Impurities (Identified, Unidentified Total), Methanesulfonic Acid Determination (titration), Water Content, Particle Size Distribution, Residue On Ignition, Residual Solvents (Genotoxic Impurities (Methyl Methanesulfonate, Ethyl Methanesulfonate, Isopropyl Methanesulfonate, Total Methanesulfonates), Microbial Limits (TAMC2 and TYMC2).

The absence of a routine test for specific solvents is not justified according to Annex 1 to CPMP/ICH/283/95, therefore supporting analytical data are awaited. The particle size acceptance criteria does not reflect validation batches results. The identified related impurities are not specified in the specification. This approach seems not correct: the individual identified impurities should be specified or all potential impurities should be considered unspecified and therefore limited to 0.10%. The specification of Methane sulfonic Acid should be tightened taking into account the results of the batches and precision and accuracy of titrimetric analysis.

Appropriate analytical method validation studies have been performed.

Enasidenib Reference standard is described and characterized.

The drug substance is stored in double low density polyethylene (LDPE) bags. The bags are closed with a tie and placed into high density polyethylene (HDPE) drums and closed. The compliance to Ph.Eur. and Regulation (EU) No 10/2011 is missing.

Stability

Stability results were provided for four batches of API manufactured at the manufacturing site () at production scale using the commercial process. The drug substance was packaged in a container closure system that simulates the commercial packaging configuration. Analytical results from testing conducted on one sample stored for up to 24 months under long-term (25°C/60%RH) and 6 months under accelerated (40°C/75%RH) conditions and on three samples stored for up 12 months under long-term (25°C/60%RH) and 6 months under accelerated (40°C/75%RH) conditions are provided.

Primary stability studies have also been conducted on three batches produced at one of the clinical manufacturing sites () using the commercial process representative drug substance.

Results show a good stability of the drug substance with no significant changes or trend in any parameter. Forced degradation studies were performed on the drug substance under acid, base, oxidation, and thermal stress conditions as part of the specificity validation for the HPLC identification, assay and related impurity method. These studies have demonstrated the method is specific for the drug substance as well as the degradation products.

A photostability study was conducted on two drug substance lots: a major degradant was observed. However, the drug substance commercial packaging can sufficiently prevent photo stress degradation as demonstrated by the data. Therefore, no additional light protection is required.

Based on the results provided, the proposed retest period of 36 months for the drug substance stored at or below 25°C in the proposed container closure system is deemed acceptable.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

Enasidenib is available as 50 mg and 100 mg free base equivalent film-coated tablets. The 50 mg tablets are presented as pale yellow to yellow oval shaped tablet, debossed ENA on one side and "50" on the other side. The 100 mg tablets have the same colour as 50 mg tablets and an oval shape. They are debossed "ENA" on one side and "100" on the other side.

The drug substance is practically insoluble in aqueous solution between pH 1.2 and pH 7.4, and it has a high permeability across Caco-2 cell. It is a BCS Class II compound.

Compatibility studies of the drug substance with all excipients used in the commercial formulation were conducted and no significant changes or trends were reported. No overage has been used.

The selected formulation and the strengths result in line with the active substance's physicochemical properties and with section 4.2 of the SPC. Idhifa is indicated for the treatment of adult patients and so no paediatric formulation is required.

The product is available in HDPE bottle with silica gel as desiccant and child resistant caps. The section 6.5 of the SmPC should specify the type of desiccant.

Pharmaceutical development

The pharmaceutical development of the drug product was planned according a risk-based approach as described in ICH Q8(R2) and ICH Q9. No design spaces were claimed for the manufacturing of Idhifa.

Various tablet formulations (have been used in clinical studies with tablet strength ranging from 5 mg to 200 mg. Formulation 3 is intended for commercial use at the 50 and 100 mg tablet dosage strengths.

Comparative dissolution testing was performed using the quality control (QC) testing dissolution media and aqueous dissolution media of pH 1.2, 4.5 and 6.8.The development of the dissolution method is provided in the dossier and the discriminatory power was evaluated by analyzing tablets prepared with intentional deviations in formulation composition or process parameters.

The proposed commercial container closure system for Idhifa immediate release film coated tablets is a high density polyethylene bottle with a desiccant and child resistant caps. The suitability of the intended container closure system should be evaluated and information detailed on desiccant should be added.

Manufacture of the product and process controls, product specification, analytical procedures, batch analysis

Manufacture

The manufacturing site will be responsible for manufacture, testing, packaging and labelling, release and stability testing. Additional manufacturers will be responsible for secondary packaging and labeling. . A flow diagram and a narrative description of the manufacturing process and in-process controls are provided.

The tablets are produced using a conventional process comprising: blending, roller compaction, tablet compression and film coating. In the manufacturing process equipment commonly available in the pharmaceutical industry has been used.

Holding time were defined for a number of drug product process intermediates.

Process controls

Critical and not critical process parameters and critical or not critical in-process controls are reported. The one critical process parameter is the roll force in the roller compaction and the one in-process control considered critical is average tablet weight. The other proposed in-process control are the average tablet hardness during the tablet compression and the coating weight gain in the film coating step. The range of the proposed in-process controls appear adequate.

No Design Space is claimed.

Process validation/ verification

The manufacturing process has been validated by three commercial batches for both the 50 and 100 mg strength using two different lots of API. All batches met all test acceptance criteria.

All excipients used in the drug product, except Opadry II Yellow, are compendial excipients which conform to European Pharmacopoeia and National Formulary.

The specifications of Opadry II Yellow are set in accordance with in-house parameters.

Stability of the product

Based on the stability data presented, the shelf life proposed for the drug product is 24 months in HDPE bottles with a desiccant and child resistant caps when stored at "Keep the bottle tightly closed. Store in the original package in order to protect from moisture".

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Drug substance

The concerned medicinal product is Idhifa (enasidenib) 50 mg and 100 mg film coated tablets.

Full information is provided in the application with respect to the active substance enasidenib mesilate. No ASMF or CEP is present.

Enasidenib (AG-221, CC-90007) is a mesylate salt of a weak base.
The commercial manufacture of enasidenib mesylate drug substance is a four stage process from the proposed regulatory starting materials.
A combination of traditional and enhanced approaches was applied during the development, though a design space is not formally claimed.
The drug substance specifications include the following controls: Appearance, Identification FT-IR, Identification HPLC, Solid Form (XRPD), Assay (HPLC), Related Impurities (Identified, Unidentified Total), Methanesulfonic Acid Determination (titration), Water Content, Particle Size Distribution, Residue On Ignition, Residual Solvents (Genotoxic Impurities (Methyl Methanesulfonate, Ethyl Methanesulfonate, Isopropyl Methanesulfonate, Total Methanesulfonates), Microbial Limits (TAMC2 and TYMC2).

Appropriate analytical method validation studies have been performed.
Based on the results provided, the proposed retest period of 36 months for the drug substance stored at or below 25°C in the proposed container closure system is deemed acceptable.
A minor issues on Drug substance quality documentation is still pending (OC).

Finished product
Enasidenib is available as 50 mg and 100 mg free base equivalent film-coated tablets.
The pharmaceutical development of the drug product was planned according a risk-based approach as described in ICH Q8(R2) and ICH Q9. No design spaces were claimed for the manufacturing of Idhifa.

The manufacturing site will be responsible for manufacture, testing, packaging and labelling, release and stability testing. Additional manufacturers will be responsible for secondary packaging and labelling.

Critical and not critical process parameters and critical or not critical in-process controls are reported.

Batch analysis data have been presented. All batches met the test limits as defined in the release specification.
Based on the stability data presented, the shelf life proposed for the drug product is 24 months in HDPE bottles with a desiccant and child resistant caps when stored at "Keep the bottle tightly closed. Store in the original package in order to protect from moisture".

3.2. Non clinical aspects

The nonclinical safety program of enasidenib followed the International Conference on Harmonization (ICH) S9 guideline for the nonclinical evaluation for anticancer pharmaceuticals.

3.2.1. Pharmacology

Mode of action

AG-221 was developed as an isocitrate dehydrogenase 2 (IDH2) inhibitor. It acts as a differentiation agent through direct suppression of 2-HG, which in turn leads to both an induction of cellular differentiation and an inhibition of cellular proliferation in IDH2-expressing tumor cells.

In vitro pharmacology studies demonstrated that enasidenib exerted its antineoplastic activity through inhibition of various mutant forms of IDH2, including the IDH2 variants R140Q, R172S, and R172K. The results of the kinetic studies demonstrated that AG-221 was more potent at inhibiting IDH2 R140Q, IDH2

R172K, and IDH2 172S mutants in comparison to IDH2 wild-type (IDH2WT) enzymes (> 40 fold difference). However, in a direct comparison (which could only be made after 1 hour) only a 2-fold increase of IDH2 R140Q versus IDH2 R172K was determined which is not considered as a real excess. Since the in vitro kinetic data are the basis for further in vivo testing it would have been helpful to perform in vivo studies in a direct comparison with both, the 140Q and 172S/K mutant. However, although there is limited availability of cell lines for studying different IDH mutant, it is agreed that IDH2-R140Q is the most prevalent variant for enasidenib. It is also agreed that enasidenib is active in both models, R140Q and R172K. The conclusion that AG-221 is more potent in models with the R140Q mutant compared to R172K have to be further justified by clinical data.

AG-221 exhibited a non-competitive inhibition against IDH2R140Q with respect to α-KG substrate and an uncompetitive inhibition with respect to NADPH. However, it remains unclear if AG-221 exhibited a significant superior inhibition of IDH2 R140Q with respect to α-KG and NADPH over IDH2 R172K since no data are available for the latter mutation.

The kinetic analysis were performed with homodimers instead of heterodimers because the forward and reverse reactions are counter-acting to each other with respect to conversion of NADP+ to NADPH. The kinetic evaluation also indicated that AG-221 exhibited a time-dependent inhibition of 2-HG. This could be shown for the 140Q mutant with maximal inhibition at 16 hours, whereas the inhibition behaviour of the 172K mutant did not change significantly between 1 and 8 hours. Literature reference was provided demonstrating that measurement of NADPH is a suitable indicator for the determination of 2-HG and as a consequence for the activity of IDH mutants. However, the question if there is a slow-off reaction or a spontaneous reduction of the enzymatic reaction remains unclear. Possible enzymatic limitations are the consumption of NADPH or consumption of αKG. In order to get more information about the kinetic involvement of the IDH mutants in the proposed pathway, the applicant provided data from two additional experiments. The results of the first study showed that the rate of NADPH consumption correlates with the concentration of both mutant proteins. Further evaluation using Michaelis-Menten kinetic revealed a saturation curve for alpha KG with both IDH2 R140Q and IDH2 R172K. Another point mentioned to underline that the proposed pathway is dependent of the two IDH2 mutant proteins is the fact that according to Gross et al. 2010, concentrations of alpha KG are the same in IDH2 mutant and wild-type AML, whereas levels of 2HG in IDH2 mutant cells can be significant higher compared to wild-type cells.

Overall, the data provided by the applicant so far underline the assumption that the production of 2HG is not alone the result of a spontaneous reaction but mainly the consequence of an enzymatic reaction of the mutant proteins IDH2 R140Q and IDH2 R172K.

Two metabolites of AG-221, AGI-16903, and AGI-17011, were also evaluated in the same system. AGI-16903 and AGI-17011 showed selectivity for the IDH2 (R140Q) mutation and weaker activity for IDH2 (R172K) and wild-type IDH2. The metabolite AGI-16903 is also present in monkeys and humans whereas the metabolite AGI-17011 has not been found in rats, monkeys and humans.

Further in vitro studies in cell lines over-expressing the IDH2 mutant R140Q (i.e., TF-1 and U87MG cells) showed that sub-nanomolar concentrations of enasidenib can reduce 2-HG levels by ≥ 95% in both cell lines in comparison with other IDH2 (≥50%) and IDH1 (≥20%) mutant isoforms. These results support the hypothesis that AG-221 may play a specific role in inhibiting IDH2 isoforms though only a limited number of IDH2 isoforms were tested.

In TF-1 cells, enasidenib reduced intracellular levels of 2-HG in a concentration-dependent manner by about 90% after 7 days of treatment. AG-221 reduced also histone hypermethylation, decreased the expression of vimentin and decreased the percentage of hematopoietic stem and progenitor cells relative

to untreated controls. In addition, cellular differentiation was induced. No significant apoptotic activity was determined.

In an ex vivo assay with primary human AML blast cells (including cells with IDH2 R140Q mutations), treatment with enasidenib for up to 9 days reduced 2-HG levels by 99% relative to controls and induced cellular differentiation as noted by the increase in metamyelocytes and a decrease of blast cells from 90% to 40% by day 9 of treatment. However, the conclusion that AG-221 reduces intracellular 2-HG and induces cellular differentiation in IDH2R140Q primary human AML bone marrow is based on a limited number of primary cells (cells from 2 patients). Updated information provided by the applicant (Yen, 2017) support a positive effect of enasidenib in patients (N=3) with AML and underline the hypothesis that enasidenib exerts its anti-tumour effect via IDH mutations. However, this conclusion should be verified in conjunction with clinical data.

Additionally, two in vivo mouse IDH2 R140Q xenograft models were conducted. In these models, treatment with AG-221 or genetic de-induction of a conditional IDH2 (R140Q) allele led to decreased expression of 2-HG (>95%) and increased percentages of cells expressing markers of differentiated myeloid cells in the bone marrow. Further, treatment with AG-221 resulted in reduced disease burden and prolonged the survival of the mice.

These data led to the Applicant suggestion that AG-221 is an effective therapeutic strategy in this AML mouse model harboring IDH2 (R140Q), NRAS (G12D), and DNMT3A (R882H) mutations. AG-221 may then be an effective treatment for patients with IDH2-mutated AML, may overcome the cellular differentiation block caused by mutant IDH2, and may inhibit the leukemogenic potential of IDH2-mutated cells, as suggested by the Applicant. The above evidence are indeed consistent with clinical phase I/II trial data, demonstrating that enasidenib inhibited the production of 2-HG and induced clinical responses in relapsed or refractory IDH2-mutant AML (Stein et al., 2017; see Clinical AR), as a result of AG-221 binding to the IDH2 dimer interface and subsequent block of 2-HG production by IDH2 mutants. Clinical resistance, disease progression, and a recurrent increase in circulating levels of 2HG following enasidenib administration has however been demonstrated (Intlekofer et al. (2018)), which is associated with the emergence of second-site mutations in trans occurring at glutamine 316 (Q316E) and isoleucine 319 (I319M), and located at the interface where enasidenib binds to the IDH2 dimer. In addition, when the second-site mutations co-occurred with IDH2-R140Q mutation in trans, high levels of 2-HG were produced despite exposure to enasidenib in vitro and in vivo. Therefore, the involvement of mutations conferring resistance to enasidenib is acknowledged. However, when evaluating the frequency of such second-site mutations, these where observed only in 3.4% patients, being not detectable at diagnosis as well. In addition, the prevalence of this resistance mechanism has not been explored in the overall trial population, and will be further analyzed in the ongoing Phase 3 study AG-221-AML-004.

A series of in vivo pharmacology studies in a U87MG IDH2 (R140Q) xenograft mouse model confirmed the potency of AG-221 in inhibiting 2-HG production in both plasma and tumor tissue. In these studies, plasma and tumor concentrations decreased rapidly following administration of AG-221 and the inhibition was dose and drug exposure dependent. Administration of 3 repeat doses of AG-221 at ≥ 50 mg/kg inhibited both plasma and tumor 2-HG levels by > 90%. However, values were presented without standard deviation which are up to and above 100% in individual cases. Therefore, the value 90% should be handled with care. Tumor 2-HG concentration was maximally suppressed by 1 hour following the third dose of AG-221 and remained suppressed through 24 hours. The 2-HG inhibition effect was sustained when the plasma concentration of AG 221 was above approximately 1000 ng/mL. Inhibition of 2-HG was also evaluated on termination in different organs. AG-221 inhibited 2-HG production in blood, plasma, spleen, urine, and bone marrow in the human IDH2R140Q leukemia xenograft model. However, at present no information is available about the time point when the 2-HG values in spleen, urine and bone

marrow were determined since some animals did not reach the day of termination (day 103). The contribution of AGI-16903 to plasma and tumor 2-HG inhibition was considered minimal.

Secondary pharmacology

AG-221 and its metabolite AGI-16903 were evaluated for their potential to inhibit binding and enzymatic activity in screening panels representing multiple receptors, ion channels, transporters, and diverse enzymes, including kinases. Enasidenib and its metabolite AGI-16903 bind adenosine A1, A2A, and A3 receptors in vitro and act as functional antagonists. The most potent functional antagonist activity for both compounds was against adenosine A3 receptor, with IC50 values of 5.7 and 120 nM for enasidenib and the metabolite, respectively.

Safety pharmacology

Enasidenib had a half-maximal inhibitory concentration (IC50) of 9.02 µM for human ether-á-go-go related gene and 16.8 µM for hCaV1.2 currents. AGI-16903, an N-dealkylated enasidenib metabolite, had an IC50 of 10.7 µM for hCaV1.2 current. In dogs, prolonged heart-rate corrected QT interval (QTc), decreased blood pressure and significantly increased heart rate were noted after single doses of 75 or 300 mg/kg and/or after repeat doses of 15 and 50 mg/kg BID for up to 7 days. At 5 mg/kg BID in dogs, above-mentioned cardiovascular changes were noted after single dose, but these changes did not persist after repeat doses for 7 days. The maximum observed plasma concentration (Cmax) at 5 mg/kg BID was 940 ng/mL, which was approximately 14-fold lower than the Cmax (12,800 ng/mL) at the recommended therapeutic dose of 100 mg QD in patients. In monkeys, no QTc prolongation and alteration in other cardiovascular parameters was seen at Cmax either comparable or 2.5- to 6.5-fold lower than clinical the Cmax indicated above. Overall, the in vitro and in vivo data do not indicate a cardiotoxic potential of enasidenib.

3.2.2. Pharmacokinetics

The PK of enasidenib is characterized by biexponential decline in plasma concentrations, with rapid oral absorption in rats, dogs and monkeys. Total body plasma clearance (CLp) was low in rats and monkeys, and moderate in dogs. The volume of distribution at steady-state was high in rats, dogs, and monkeys. The t½ was moderate to long in rats, dogs and monkeys. Oral bioavailability of the free base form was approximately 40% to 50% in all species. Enasidenib mesylate salt improved enasidenib exposure over the free-base form in oral rat PK studies. Plasma exposure to enasidenib in monkeys after oral dosing of mesylate salt under fasting conditions was 1.9-fold higher than exposure under fed conditions. In healthy volunteers, enasidenib has much longer t½ (approximately 30 hours) than in nonclinical species, and the absolute bioavailability was approximately 57% following 100 mg oral dose.

Enasidenib-derived radioactivity was rapidly absorbed and widely distributed into tissues, following a single oral (10 mg/kg) dose of $^{[14C]}$enasidenib to male and female albino SD rats. The highest concentrations of radioactivity in tissues at Tmax were found in small intestine, liver, stomach (glandular and non-glandular), kidney cortex, adrenal gland, Harderian gland, pancreas, and adipose (brown). The lowest concentrations of radioactivity were seen in the tissues of the central nervous system (cerebellum, cerebrum, medulla, and spinal cord) and bone. Elimination was nearly complete at 168 hours post dose, with the radioactivity content below the quantification limit (0.087 µg-equivalent/g) by 96 hours post dose for most tissues. In pigmented LE rats, the concentrations in eye uveal tract and pigmented skin suggested association of $^{[14C]}$enasidenib-derived radioactivity with melanin-containing tissues. However, the decreasing concentration observed in pigmented tissues suggested that the association with melanin was reversible.

Plasma protein binding was high in all species for both enasidenib and its metabolite AGI-16903 (M1).

The results from in vitro and in vivo studies demonstrate that enasidenib is mainly metabolized through N-dealkylation, oxidation, direct glucuronidation, and combinations of these pathways. In vitro data indicate that N-dealkylation to form M1 is the prominent pathway in dogs, monkeys and humans, while hydroxylation to form M2 is the prominent pathway in rats. All the metabolites formed in humans were formed in one or more animal species used for safety evaluation. In human, M1 is the most notable circulating metabolite.

Quantification of metabolite M1 in rat and monkey toxicology studies and humans indicates that human M1 exposure at therapeutic enasidenib dose levels is greater than M1 exposure in rat at STD10 dose, but lower than M1 exposure in monkey at NOAEL dose of enasidenib. These data indicates that the prominent human metabolite M1 is not a disproportionate metabolite and adequate coverage was demonstrated in monkeys.

In rat, excretion of $^{[14C]}$enasidenib-derived radioactivity is rapid and virtually complete. Fecal route is the major excretion pathway with > 85% of the administered dose recovered, while urinary excretion is a minor pathway, representing < 12% of the administered oral dose. Biliary route of excretion is the major excretory pathway for the absorbed fraction of the radioactivity in rats, with a recovery of approximately 35% to 42% of the administered oral dose of $^{[14C]}$enasidenib. In humans, excretion is comparable to that in rat for enasidenib-derived radioactivity, with a mean of 73.9% recovered in feces and 8.47% recovered in urine, with a mean total recovery of 82.4%. In humans, < 25% of the administered dose was excreted as the parent drug. These data indicate that enasidenib has good absorption in rats and humans, and hepatobiliary elimination appears to be the predominant route of enasidenib clearance.

Enasidenib and its metabolite AGI-16903 are inhibitors of several CYP isoforms with IC_{50} values < 10 µM. In addition, enasidenib and AGI-16903 also inhibit several transporters with IC_{50} values < 1 µM. In humans at 100 mg dose, the Cmax was approximately 27 µM for enasidenib and 2.9 µM for AGI-16903. At 200 mg dose, the Cmax was approximately 37 µM for enasidenib and 4.5 µM for AGI-16903. These data suggest that enasidenib may cause pharmacokinetic interactions when co-administered with drugs that are substrates of those CYPs and transporters. The clinical relevance of these findings has not been studied in a clinical drug interaction study. Based on the in vitro data for enasidenib interactions with CYP isoforms, UGT1A1, and transporters, appropriate recommendations to manage potential drug-drug interaction are included in clinical sections. Inhibition of UGT1A1 by AG-221 was investigated. As glucuronidation represents one of the major metabolism pathways, UGT2B7 inhibition by AG-221 will also be investigated and the data will be provided when available.

3.2.3. Toxicology

Repeat dose toxicity

Gastrointestinal toxicity in enasidenib-treated animals (GI atrophy/erosions in rats and emesis, diarrhea, soft/mucoid feces, inappetence, and ulcerative inflammation in large intestine in monkeys) was dose limiting. In rats, dogs, and monkeys, enasidenib-related reversible serum bilirubin increases were consistently seen in all studies. UGT1A1 inhibition by enasidenib was the likely cause of increased serum bilirubin. There were no other relevant clinical pathology or histopathology findings in animals associated with increased serum bilirubin that would indicate cholestasis or liver injury as a cause for the increased serum bilirubin.

Rats did not tolerate 100 mg/kg BID. Doses of ≤ 30 mg base/kg BID were tolerated. Enasidenib treatment-related target organs toxicity included GI tract, liver, lung, lymphoid tissues, skeletal muscle, pancreas, kidney, urinary bladder, adrenal, pituitary, salivary and mammary glands, bone (physis/cortex), and/or male and female reproductive organs. At 100 mg/kg BID, severities and incidences of target organ toxicities were significantly higher compared to 30 mg/kg BID. At 20 and 5

mg/kg BID, target organ toxicities were limited to male reproductive organs (testes/epididymides) and pancreas. Due to adverse histopathologic changes in testes/epididymides observed at 20 mg/kg BID compared to 5 mg/kg BID the NOAEL in the 90-day toxicity study in rats (longest treatment duration) was 5 mg/kg BID for males (Day 90 $AUC_{0\text{-}24hr}$ of 25000 ng·hr/mL) and 20 mg/kg BID for females (Day 90 $AUC_{0\text{-}24hr}$ of 354000 ng·hr/mL). These Day 90 enasidenib free base exposure values in males and females are approximately 0.10- and 1.40- fold, respectively, of clinical exposure.

Dogs were treated with AGI-14405, enasidenib phosphate pro-drug as it showed better oral exposure compared to enasidenib free base earlier in the nonclinical program. Dosing duration in the repeat-dose dog toxicity study was limited to 7 days. In this study, mortality occurred at 50 mg/kg BID and doses of ≤ 15 mg/kg BID were tolerated. Significant test article-related toxicities included increased heart rate, decreased PR and RR intervals, prolongation of QTcV interval and arterial degeneration/necrosis in the heart. Although blood pressure was not measured in this study, decreased blood pressure was observed in a single dose safety pharmacology study in dogs. At the MTD of 15 mg/kg BID, Day 6 Enasidenib free base exposure ($AUC_{0\text{-}24hr}$) of 13800 ng·hr/mL was approximately 0.05-fold of clinical exposure.

Arterial lesions noted in enasidenib-treated dogs were consistent with similar lesions reported in dogs treated with different vasoactive drugs. Dogs are considered particularly sensitive to cardiovascular toxicity associated with vasoactive modulation. One possible contributing cause for enasidenib-related cardiovascular findings in dogs may relate to a vasomodulatory effect, whereby decreased blood pressure (up to 21 mm Hg decrease vs. pretest) and increased heart rate (up to 67 beats per minute increase vs. pretest) were noted in enasidenib-treated dogs.

Monkeys did not tolerate doses of ≥ 12 mg/kg BID. Doses of ≤8 mg/kg BID were tolerated. Enasidenib treatment-related target organs of toxicity included large intestine, coronary arteries and arteries of other tissues, lymphoid tissues, bone marrow, kidney, liver, adrenal gland, pancreas, and femur/tibia. In the 90-day toxicity study in monkeys (longest treatment duration), microscopic changes were limited to thymus, liver, pancreas, bone marrow, and femur/tibia and were attributed to the secondary effect of enasidenib-related decrease in body weight and food consumption. Thus, the NOAEL in the 90-day toxicity study in monkeys was 6 mg/kg BID with a Day 90 $AUC_{0\text{-}24hr}$ of 88800 ng·hr/mL. The Day 90 enasidenib free base exposure value is approximately 0.34-fold of clinical exposure. The steady state exposure of AGI-16903, the most notable circulating metabolite of enasidenib in humans, in the 90-day toxicity study in monkeys exceeded its steady state exposure obtained in humans.

The cause for enasidenib-related CV changes is uncertain. Off-target selectivity screening did not reveal a cause. Enasidenib antagonizes adenosine receptor activities and in toxicology studies, free enasidenib Cmax values (3262 ng/mL, highest value) exceeded the IC_{50} values (2.7 through 1400 ng/mL) for different adenosine receptor antagonism. However, based on the known effects (mast cell response, alteration of ocular pressure, dieresis, natriuresis, etc.) of different adenosine receptor antagonism, which were not seen in enasidenib toxicology studies, such adenosine receptor-associated effect is unlikely to be responsible for the enasidenib-related CV changes seen.

Genotoxicity and Carcinogenicity

Enadisenib was negative in in vitro Ames tests and chromosome aberration assays in CHO cells and in an in vivo micronucleus test performed in rats. Thus, enadisenib is not considered to be genotoxic in vitro and in vivo. In line with ICH S9 carcinogenicity studies with enasidenib were not performed.

The Applicant also stated that the AGI-16903 metabolite, does not possess a structural alert of mutagenicity, based on an *in silico* evaluation using quantitative structure-activity relationship (QSAR) genetic toxicity predictive tools.

Reproductive and Developmental Toxicity

Pivotal reproductive and developmental toxicity testing of enasidenib was carried out in compliance with GLP and according to ICH Guideline S9. Therefore studies with substance induced effects on fertility and early embryonal development (Segment I) as well as pre- and postnatal development (Segment III), were not conducted.

The rat was used in single and repeated dose (14 / 28 / 90) d toxicology studies with dose dependent histopathologic changes in testes, epididymis, and ovaries. In the 90 d repeat dose toxicity study exposures ($AUC_{0\text{-}24h}$) at NOAEL were 25 µg h/ml for males and 354 µg h/ml for females. Compared to the clinical exposure (AG221-C-001, 100mg/d, $AUC_{0\text{-}24h\ cycle\ 2/d1}$ 258.51 µg h/ml) exposure margins were 0.1 for males and 1.4 for females. Potential effects of enasidenib on male and female fertility cannot be excluded. This should be properly reflected in the section in section 4.6 (fertility) and 5.3 in the SPC of Idhifa.

Enasidenib was neither teratogenic in rat nor rabbit under the conditions of the studies at exposures significantly below the clinical exposures based on AUC. A teratogenic risk for humans at clinical exposures could not be estimated. Enasidenib caused embryotoxicity (increased fetal skeletal developmental variations of sternebrae not ossified, decreased litter size and number of viable fetuses per litter, increase in early and late resorptions and postimplantation loss, decreased mean gravid uterine weights) in rats. All findings were accompanied by maternal toxicity (decreases in body weight, body weight gain and food consumption) at exposures below clinical exposures based on AUC. Enasidenib caused embryotoxicity (increase in postimplantation loss, abortions, and reduced fetal body weights) in rabbits. All findings were accompanied by maternal toxicity (decreases in body weight, body weight gain and food consumption) at exposures below clinical exposures based on AUC. This should be properly reflected in section 4.6 and 5.3 in the SPC of Idhifa.

The wording of 4.6 and 5.3 in the SPC should be in line with the current ICH SPC "Guideline on risk assessment of medicinal products on human Reproduction and lactation: from data to labelling" (EMEA/CHMP/203927/2005).

Phototoxicity

In a tissue distribution study in rats using a single oral (10 mg/kg) dose of [^{14}C]AG-221, test article-related radioactivity in ocular tissues (8.5 µg equivalent/g) and skin (4.5 µg equivalent/g) of pigmented Long-Evans rats were higher than that detected in ocular tissues and skin (≤3.8 µg equivalent/g) of albino SD rats suggesting an (reversible) association of enasidenib with melanin-containing tissues (see pharmacokinetics for details).

In line with ICH S10 an in vitro phototoxicity assay was performed to exclude any phototoxic potential of enasidenib. The initial dose range finding assay using up to 100 µg/mL enasidenib yielded an IC_{50} +UVR of 21.83 µg/mL, an IC_{50} –UVR could not be determined. However, precipitation was noted at 31.6 µg/mL. Therefore, the final assay was performed in quadruplicate with a concentration range of 0.5 to 31.6 µg/mL -UVR and +UVR. The Applicant used enadisenib in this concentration range since enasidenib precipitated at 100 µg/mL. Assays 1 and 2 were not considered to be valid due to unacceptable variations in concentrations of the used formulations. Based on the remaining assays 3 and 4 the applicant concluded that enasidenib is not phototoxic. As IC_{50} values could not be determined –UVR, C_{max} values (31.6 µg/mL) were used for PIF calculations resulting in PIFs slightly above 1, what might indicate phototoxicity. However, as MPE values are < 0.15, the applicant concludes that enasidenib is not phototoxic. This approach, however, appears to be unreliable. A concentration of 31.6 µg/mL enasidenib does not lead to cytotoxicity –UVR. When UVR is applied, cytotoxicity is notable, however, concentration response curves are incomplete and do not reach the bottom. This has two implications: Firstly, for IC_{50} calculations curves have to be extrapolated to zero leading to uncertainties in the obtained values. Secondly, applying C_{max} values of incomplete curves

instead of true IC_{50} values (-UVR) for PIF calculations leads to lower PIF values. The same is true for MPE calculations. This mathematical model compares the whole range of the concentration response curves. However, if curves are not recorded completely, this will result in uncertainties in the obtained MPE values as curves will have to be extrapolated. After UVR irradiation the curve starts descending at 10 µg/mL (beginning of cytotoxicity). This concentration is in the range of C_{max} values reached in clinical trials of 13 µg/mL (100 mg enasidenib QD, AG221-C-001). To date, in humans, 6 cases of mild to moderate photosensitivity reactions (3 of them were possibly treatment-related) were reported out of approximately 2000 human subjects including relapsed or refractory acute myeloid leukemia (AML) patients exposed to enasidenib in clinical trials, compassionate-use program, investigator-initiated trials (IITs), and post-marketing settings. Therefore, the risk of enasidenib-related phototoxicity in humans is considered to be minimal.

Impurities/metabolites

A total of 47 processes-related compounds have been evaluated for mutagenic potential with in silico models (QSAR, Derek Leadscope). From these, 14 impurities were predicted to have a mutagenic potential. For one of these impurities, 2,2-dimethyloxirane, published literature of a positive Ames test is available (Cornet et al, 1992). The remaining 13 impurities were subsequently tested in GLP-compliant Ames assays. All of these impurities were negative in the performed Ames assays and can be considered as not-genotoxic. For specifications of these impurities please refer to the quality assessment reports. For these 14 impurities and the metabolite AGI-16903 reports of these QSAR analysis or bibliographic references have not been provided by the applicant. Therefore, the applicant is asked to clarify and provide these reports (**OCs**).

3.2.4. Ecotoxicity/environmental risk assessment

The applicant provided an ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, 2006, corr 2). The ERA stops in Phase I of the assessment. The study on $logK_{OW}$ is acceptable and no further PBT assessment is necessary. The PEC calculation is acceptable. No further assessment in Phase II is required. Considering these conclusions enasidenib mesylate is not expected to pose a risk to the environment.

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log P_{ow}	OECD107	4.1 (pH 4) 4.0 (pH 7) 4.1 (pH 9)	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0022	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			N

3.2.5. Discussion on non-clinical aspects

Pharmacology

In vitro pharmacology studies demonstrated enasidenib was more potent at inhibiting IDH2 R140Q, IDH2 R172K, and IDH2 172S mutants in comparison to IDH2 wild-type (IDH2WT) enzymes (> 40 fold

difference). For the kinetic evaluation homodimers were used and the IC 50 values were determined at different time points for IDH2 R140Q and IDH2 R172K/S molecules. For this reason, a direct comparison could only be made after one hour.

The relative potency of AG-221 did not change over a period of 8 hours for IDH2 R172K and it is stated that this is also the case for the IDH2 R172S mutant but this assumption wasn't proven. Based on the data it remains speculative that both IDH2 R172 mutants behave identical over time. Furthermore, comparing the IC50 values at one hour showed only a two-fold potency of IDH2 R140Q over IDH2 R172K and represents not a clear advantage for IDH2 R140Q over IDH2 R172K. In addition, it is not clear if there is a slow-off action or a spontaneous reduction after 16 (IDH2 R140Q) or 8 (IDH2 R172K) hours after binding of AG-221 to the IDH2 mutants. Further, it is not obvious why the kinetic evaluation was conducted with mutant homodimers since according to Yen et al, the heterodimer produces 2-HG more efficiently than mutant homodimers and were therefore more important. And still the point that the co-occurrence of other amino acid substitutions may influence the effect of AGI-221 were not discussed in detail.

In vitro studies in cell lines over-expressing the IDH2 mutant R140Q (i.e., TF-1 and U87MG cells) showed that sub-nanomolar concentrations of enasidenib can reduce 2-HG levels by ≥ 95% in both cell lines in comparison with other IDH2 (≥50%) and IDH1 (≥20%) mutant isoforms. However, only a limited number of IDH2 isoforms were tested and therefore a generalizing statement may be premature. It is however agreed that treatment with enasidenib resulted in an anti-tumour effect in the used cell lines. In TF-1 cells, enasidenib reduced histone hypermethylation and decreased the percentage of hematopoietic stem and progenitor cells relative to untreated controls, and induced cellular differentiation. Inhibition of the IDH2 mutants has therefore a positive effect on the biology of the mutated cells. However, it remains unclear whether inhibition of the mutant enzyme can restore normal epigenetic patterning and translate into clinical efficacy. In an ex vivo assay with primary human AML blast cells (including cells with IDH2 R140Q mutations), treatment with enasidenib for up to 9 days reduced 2-HG levels by 99% relative to controls, decreased the number of viable AML blast cells (55-99% by Day 6) and induced cellular differentiation as shown by changes in cell surface markers (CD14, CD15 and CD11b) associated with monocytic and granulocytic differentiation. However, this conclusion is based on a limited number of primary cells and since no information is available of the R172 mutated enzyme, it seems questionable if this result could be the basis for an assumption of selective activity. Additionally, in IDH2 R140Q xenograft models, treatment with enasidenib dose-dependently decreased serum 2-HG levels (>95%), increased blast cell differentiation in the bone marrow, and prolonged the survival of the mice for a short term only. The 2-HG inhibition effect was sustained when the plasma concentration of AG-221 was above approximately 1000 ng/mL.

Enasidenib and its metabolite AGI-16903 bind adenosine A1, A2A, and A3 receptors in vitro and act as functional antagonists. The most potent functional antagonist activity for both compounds was against adenosine A3 receptor, with IC50 values of 5.7 and 120 nM for enasidenib and the metabolite, respectively.

Enasidenib inhibits hERG and Cav1.2 currents with IC_{50} values of 9 µM and 10 – 17 µM, respectively. These values are 20 – 30-fold higher compared to therapeutically effective free plasma concentrations in humans (about 0.5 µM, due to its high plasma protein binding of 98.5 %). In dogs, frequency-corrected QT interval prolongation (QTcV) was observed after oral doses of 75 – 300 mg/kg with a delay of > 4 hours at plasma concentrations comparable to those obtained in humans; it is not clear whether these effects are due to possible effects of enasidenib on the trafficking of cardiac ion channels (represented by its delayed appearance) or are an artefact (since these effects were not dose-related and only observed in 1 animal). The weak effects of enasidenib on cardiac ion channels together with the absence of ECG effects in monkeys at oral doses of up to 25 mg/kg and the unclear and relatively minor delayed

effects of enasidenib on the QTcV interval in dogs do not seem to indicate a cardiotoxic potential of enasidenib.

Pharmacokinetics

In vitro and in vivo absorption, distribution, metabolism, and excretion (ADME) studies of enasidenib have been conducted. In addition, in vitro studies were performed to evaluate the potential for pharmacokinetic drug-drug interactions. There are also single studies investigating the PK of the main active human metabolite M1. Quantification of M1 in rat and monkey toxicology studies and humans indicates that human M1 exposure at therapeutic enasidenib dose levels is greater than M1 exposure in rats, but lower than M1 exposure in monkey at NOAEL dose of enasidenib. These data indicate that adequate coverage of the prominent human metabolite M1 was demonstrated in monkeys.

Overall, the PK of enasidenib and M1 in nonclinical species used for toxicity testing were adequately characterized. Based on the in vitro data for enasidenib interactions with CYP isoforms, UGT1A1, and transporters, appropriate recommendations to manage potential drug-drug interaction are included in clinical sections.

Toxicology

Gastrointestinal toxicity in enasidenib-treated animals (GI atrophy/erosions in rats and emesis, diarrhea, soft/mucoid feces, inappetence, and ulcerative inflammation in large intestine in monkeys) was dose limiting. In rats, dogs, and monkeys, enasidenib-related reversible serum bilirubin increases were consistently seen in all studies.

In pivotal repeat-dose toxicity studies in rats, the main enasidenib dose-related findings at sub-therapeutic exposures included GI tract, liver, lung, lymphoid tissues, skeletal muscle, pancreas, kidney, urinary bladder, adrenal, pituitary, salivary and mammary glands, bone (physis/cortex), and/or male and female reproductive organs. Due to adverse histopathologic changes in testes/epididymides observed at 20 mg/kg BID compared to 5 mg/kg BID the NOAEL in the 90-day toxicity study in rats (longest treatment duration) was 5 mg/kg BID for males (Day 90 $AUC_{0\text{-}24hr}$ of 25000 ng·hr/mL) and 20 mg/kg BID for females (Day 90 $AUC_{0\text{-}24hr}$ of 354000 ng·hr/mL). These Day 90 enasidenib free base exposure values in males and females are approximately 0.10- and 1.40- fold, respectively, of clinical exposure.

Monkeys did not tolerate doses of ≥ 12 mg/kg BID. Enasidenib treatment-related target organs of toxicity included large intestine, coronary arteries and arteries of other tissues, lymphoid tissues, bone marrow, kidney, liver, adrenal gland, pancreas, and femur/tibia. In the pivotal 90-day toxicity study in monkeys (longest treatment duration), microscopic changes were limited to thymus, liver, pancreas, bone marrow, and femur/tibia and were attributed to the secondary effect of enasidenib-related decrease in body weight and food consumption. Thus, the NOAEL in the 90-day toxicity study in monkeys was 6 mg/kg BID with a Day 90 $AUC_{0\text{-}24hr}$ of 88800 ng·hr/mL. The Day 90 enasidenib free base exposure value is approximately 0.34-fold of clinical exposure.

The steady state exposure of AGI-16903, the most notable circulating active metabolite of enasidenib in humans, in the 90-day toxicity study in monkeys exceeded its steady state exposure obtained in humans.

Reports for QSAR analysis and bibliographic references of metabolite AGI-16903 and process-related impurities have been included in the dossier.

Enasidenib is taken up into melanin containing tissues in rats and based on the uncertain results (PIF, MPE values) of the in vitro phototoxicity assay and the phototoxicity observed at concentrations in the range of the clinical C_{max} of 13 µg/mL, the applicant the applicant is requested to discuss the possibility of proper labelling of potential phototoxicity in the SmPC. Furthermore, if the company seeks widening

of the indication, e.g. for first line treatment, phototoxicity might become relevant and as a consequence it might be necessary to provide a dedicated clinical phototoxicity study.

Conclusion on non-clinical aspects

The applicant has submitted a non-clinical set of data aimed to characterise the pharmacology, pharmacokinetics, and toxicology of enasidenib.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Table clin 01. Overview of All AG-221 (Enasidenib) Clinical Studies with Pharmacokinetic Data

Study	Brief Description
Phase 1 Studies that Define PK Characteristics in Healthy Subjects	
Food effect (AG221-C-002)	Healthy male. Dose: Single oral dose crossover of 100 mg AG-221 (F2, Tablet). Enrolled/completed with PK data: 30/29 subjects.
PK in Japanese relative to Caucasian (AG-221-CP-001)	Healthy male. Dose: Single oral dose of 50 mg, 100 mg and 300 mg AG-221 (F3, Tablet). Enrolled/completed with PK data: 62/61 subjects.
AG-221 ADME and absolute bioavailability (AG-221-CP-002)	Healthy male. Dose: Part 1: single oral dose 100 mg AG-221 (solution containing [^{14}C]AG- 221 (300 nCi)). Part 2: single oral dose of 100 mg AG-221 (F3, tablet), and IV bolus of 100 µg AG-221 containing ~300 nCi of [^{14}C]AG-221. Enrolled/completed with PK data: 8/8 subjects (Part 1), 6/6 subjects (Part 2).
Phase 1/2 Studies that Define PK Characteristics in Patients with Advanced Hematologic Malignancies Associated with an IDH2 Mutation	
AG-221 safety, PK, PD, and clinical activity (AG221-C-001 Phase 1 and AG221-C-001 Phase 2)	Patients with relapsed or refractory advanced hematologic malignancies Dose: multiple oral doses at daily dose from 50 mg to 650 mg (F1, F2, and F3, tablet) Enrolled/completed with PK data: 344/332

Table clin 02. Clinical efficacy studies pertinent to the claimed indication

Study ID **Country**	**Study Design and key endpoints and main inclusion criteria**	**Treatment Groups, No. of Subjects** (by Treatment Group)	**Demographics** (R/R AML subjects with enasidenib 100 mg/day)	**Study Start, End/Status (Available results)**
Phase 1/2 trial				
AG221-C-001 phase 1: USA (13 centres), France (2 centres) phase 2: USA (17 centres), France (3 centres)	Study Phase: Phase 1/2 Study design: uncontrolled, open-label, multi-centre *phase 1:*	N = 345 (N= 214 wit R/R AML with 100 mg/day) phase 1: N = 239 (n=175 wit R/R AML; N= 109 with R/R AML with enasidenib 100 mg/day)	214 subjects (109 males and 105 females) median age was 68 years (range: 19 to 100)	Study start date: 20 Sep 2013 (phase 1) 25 Jun 2015 (phase 2) Data cut-off: 01 Sep 2017

	dose escalation and dose expansion (to further evaluate safety and efficacy in subjects with advanced haematologic malignancies) *phase 2:* to assess efficacy of enasidenib at the RP2D in subjects with R/R AML carrying an IDH2 mutation main efficacy endpoints: ORR (INV), CR, CR/CRi/CRp, OS, transfusion independence main inclusion criteria: IDH2-mutated advanced haematologic malignancies (not identical between dose escalation, dose expansion and phase 2 part of the study) (in the course of the study focus on R/R AML)	*dose escalation:* The following doses administered BID on Days 1 to 28 in 28-day cycles: 30, 50, 75, 100, 150 mg The following doses administered QD on Days 1 to 28 in 28-day cycles: 50, 75, 100, 150, 200, 300, 450, 650 mg *dose expansion:* enasidenib starting dose of 100 mg QD on Days 1 to 28 in 28-day cycles phase 2: N = 105 (all R/R AML with enasidenib 100 mg QD) enasidenib starting dose of 100 mg QD on Days 1 to 28 in 28-day cycles		Status: Full CSRs completed for 01 Sep 2017 data cut-off. Recruitment: complete; Treatment ongoing for a total of 16 subjects (dose escalation n=2, dose expansion n=8, phase 2 n=6); study ongoing for a total of 54 subjects (dose escalation n=12, dose expansion n=24, phase 2 n=18).
Phase 3 trial				
AG-221-AML-004 As of Apr 2018: 126 centres in 18 countries (Austria, Belgium, Czech Rep, Denmark, France, Germany, Italy, Spain, UK, USA, Australia, Canada, Turkey, South Korea, Taiwan, Russia, China, Brazil)	Study Phase: Phase 3 Study design: multicentre, randomized (1:1), open-label primary endpoint: OS main inclusion criteria: ✓ ≥ 60 years of age ✓ primary or secondary AML ✓ relapsed or refractory after second- or third-line intensive/ low-intensity AML therapy ✓ confirmed IDH2 mutation	The study design requires 250 deaths and 316 subjects (158 per treatment arm) to be randomized in order to achieve 80% power to detect a constant HR of 0.7 and demonstrate a statistically significant difference in OS versus CRR at a Type I error rate of 0.05 (two-sided). Experimental arm: Enasidenib (PO) + BSC Control arm: conventional care regimens (CCR), which include best supportive care (BSC) only, azacitidine (SC) plus BSC, low-dose cytarabine (SC) plus BSC or intermediate-dose cytarabine (IV) plus BSC	No trial results yet	

3.3.1. Pharmacokinetics

Enasidenib (INN; ATC-code[1]: L01XX59) is a small molecule inhibitor of the isocitrate dehydrogenase 2 (IDH2) mutant enzyme. During the development, it was also referred to as AG-221 mesylate, CC-90007, AGI-12910, AGI-12910 mesylate, and AG-221.

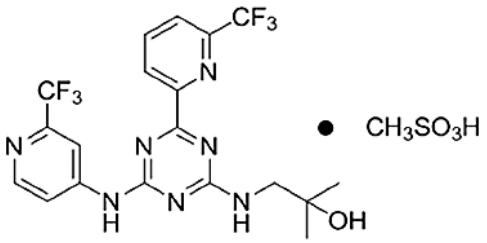
Enasidenib chemical name: 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin- 2-yl]-6-{[2-trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate

Molecular Formula: $C_{19}H_{17}F_6N_7O \bullet CH_3SO_3H$

Molecular Weight: 569.48 g/mol

Chirality: Achiral

Structural formula



Enasidenib (AG-221) has been studied clinically with oral doses ranging from 50 mg to 300 mg in healthy volunteers and multiple doses ranging from 50 mg to 650 mg daily in patients with advanced hematologic malignancies associated with IDH2 mutation.

The clinical development programme included clinical studies with overall 4 formulations for AG-221. The tablet formulation F3 is the intended to-be-marketed (commercial use) formulation and the one currently marketed in the United States.

The drug product is supplied as film-coated tablet in dose strengths of 50 mg and 100 mg.

The recommended dosing regimen is 100 mg taken orally once daily until disease progression or unacceptable toxicity.

Population PK and exposure-response analyses were conducted based on cumulative data (AG-221-MPK-001). The objectives of population PK and exposure response (efficacy/safety) analyses were:

(1) to develop a population model describing the PK data of AG-221, and associated inter-individual/residual variability in healthy subjects and patients with advanced hematologic malignancies;

(2) to assess the influence of covariates of interest on the PK of AG- 221;

(3) to predict Bayesian individual exposure for exposure-response analysis;

(4) to quantitatively describe the AG-221 exposure-response relationship in patients with advanced hematologic malignancies.

[1] https://www.whocc.no/atc/lists_of_new_atc_ddds_and_altera/new_atc/

Population PK and exposure-response analyses were presented in an updated/amended Clinical PK/PD Report (AG-221-MPK-001) dated 03 Jan 2019.

A metaanalysis, pooling PK data from both healthy subjects (AG221-C-002 and AG-221-CP-001) and subjects with advanced hematologic malignancies (AG221-C-001), has been conducted to assess the impact of different formulations on enasidenib pharmacokinetic (PK) exposure (Clinical PK Report AG-221-MPK-002).

No IVIVC has been established for enasidenib.

Enasidenib (AG-221) has been studied clinically with oral doses ranging from 50 mg to 300 mg in healthy volunteers and multiple doses ranging from 50 mg to 650 mg daily in patients with advanced hematologic malignancies associated with IDH2 mutation.

Enasidenib is rapidly absorbed by Caco-2 cells *in vitro* (Study AG221-N-031-R). However, its bioavailability, as determined in an ADME study (AG-221-CP-002), was largely incomplete, its value being 57.2%.

In healthy subjects under fasting conditions, enasidenib is readily absorbed following oral administration of a single dose of 100 mg, with median time to maximum plasma concentrations (T_{max}) of 3 to 4 hours postdose. PK exposure of AG-221 and its metabolite AGI-16903 for Caucasians and Japanese subjects were comparable at the 50, 100, and 300 mg dose levels, statistical analysis showed that the 90% CIs of geometric mean ratios for AUCs and C_{max} generally contained 100%. The systemic exposure of AG-221 and AGI-16903 appeared to be approximately dose proportional in Japanese and Caucasian in the dose range of 50, 100 and 300 mg.

Table pk 1 Geometric Mean (Geometric CV%) AG-221 Plasma Pharmacokinetic Parameters Data When Administered as a Single 50, 100 and 300 mg Oral Dose in Healthy Japanese and Caucasian Males

Cohort	Dose (mg)	Race	AUC_t (ng•h/mL)	AUC_∞ (ng•h/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	CL/F (mL/h)	V_z/F (mL)
B	50	Japanese (n=10)	21800 (46.9)	21900 (46.7)	533 (41.0)	3.98 (0.98, 8.95)	21.1 (31.6)	2290 (46.7)	69700 (40.9)
		Caucasian (n=9)	17800 (55.0)	18000 (55.0)	406 (34.9)	4.00 (2.02, 24.0)	23.0 (47.4)	2780 (55.0)	92300 (44.5)
A	100	Japanese (n=11)	40500 (47.2)	40700 (47.3)	786 (27.1)	4.00 (1.97, 24.0)	19.5 (45.6)	2460 (47.3)	69000 (25.1)
		Caucasian (n=10)	49200 (27.5)	49500 (27.8)	822 (38.5)	2.99 (1.03, 9.08)	25.5 (51.4)	2020 (27.8)	74400 (41.2)
C	300	Japanese (n=10)	168000 (44.7)	170000 (44.6)	2030 (34.3)	13.4 (1.00, 48.0)	27.7 (35.6)	1760 (44.6)	70300 (15.3)
		Caucasian (n=10)	163000 (44.8)	163000 (44.9)	1780 (27.8)	10.5 (1.97, 24.0)	28.3 (32.0)	1840 (44.9)	74900 (26.9)

AUC = area under the concentration-time curve; AUC_t = AUC from time zero to time t, where t is the last measurable time point; AUC_∞ = AUC from time zero extrapolated to infinity; CL/F = apparent total plasma clearance; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation; $t_{1/2}$ = estimate of the terminal eliminationhalf-life; T_{max} = time to C_{max}; V_z/F = apparent total volume of distribution.
[a] Median (minimum, maximum) presented for T_{max}.
Note: Cohorts: A = Single oral dose of 100 mg AG-221, B = Single oral dose of 50 mg AG-221, C = Single oral dose of 300 mg AG-221.

PK of AG-221 was further evaluated in a Phase 1/2, multicentre, open-label, 3-part (Phase 1 dose escalation, Phase 1 Part 1 Expansion, and Phase 2), safety, PK, PD, and clinical activity study of orally

administered AG-221 in subjects with advanced hematologic malignancies that harbour an isocitrate dehydrogenase(IDH) 2 mutation (AG-221-C-001-PKPD). Following a single oral dose of AG-221 at dose levels ranging from 30 to 450 mg, AG-221 was rapidly absorbed. After reaching peak levels, mean AG-221 concentrations declined in a mono-exponential manner and were detectable up to 72 hours post-dose.

Table 2 pk Geometric Mean (Geometric CV%) Plasma Pharmacokinetic Parameters of AG-221 after a Single Oral Dose of AG-221 – Phase 1 – Dose Escalation and Part 1 Expansion (Day -3)

Plasma PK Parameters[a]	30 mg (N=4)	50 mg (N=9)	75 mg (N=9)	100 mg (N=58)	150 mg (N=8)	200 mg (N=11)	300 mg (N=6)	450 mg (N=2)	650 mg (N=1)
AUC_{0-8} (ng*h/mL)	3364 (59.7);4	3020 (58.4);9	5319 (57.0);9	6634 (79.6);58	9397 (32.1);8	11550 (49.2);11	15268 (42.0);6	15039 (NR);2	31580 (NC);1
AUC_{0-10} (ng*h/mL)	4120 (61.5);4	3925 (58.4);9	6834 (54.1);9	8616 (76.5);57	11819 (31.3);8	14818 (49.2);11	20727 (41.0);6	19961 (NR);2	38711 (NC);1
AUC_{0-24} (ng*h/mL)	8987 (72.1);4	9611 (59.6);9	17330 (50.6);9	21656 (55.6);56	28989 (29.6);8	37703 (48.3);11	58743 (41.5);6	60846 (NR);2	NC
AUC_{0-72} (ng*h/mL)	19192 (138.4);3	20598 (79.9);7	37737 (53.9);8	58670 (59.5);51	76820 (31.2);8	95217 (57.2);9	160083 (12.0);4	244130 (NC);1	NC
AUC_{0-t} (ng*h/mL)	17575 (105.1);4	19975 (68.6);9	39345 (51.9);9	53018 (74.2);58	76820 (31.2);8	95959 (50.5);11	134094 (32.6);6	157042 (NR);2	38711 (NC);1
C_{max} (ng/mL)	569 (45.6);4	545 (64.0);9	1084 (51.6);9	1279 (56.1);58	1624 (29.5);8	2082 (46.5);11	3358 (43.1);6	3031 (NR);2	4670 (NC);1
T_{max}[b] (h)	1.59 (1.00 - 4.08);4	5.83 (1.92 - 24.25);9	3.00 (1.13 - 21.42);9	4.00 (0.67 - 71.97);58	3.98 (2.00 – 24.00);8	4.08 (1.00 - 48.55);11	8.89 (2.95 - 72.17);6	18.61 (13.33 - 23.88);2	6.17 (6.17 - 6.17);1
T_{last}[b] (h)	71.27 (47.88 - 73.12);4	69.50 (48.50 - 73.42);9	71.13 (48.05 - 73.75);9	71.83 (9.58 - 75.95);58	71.98 (70.10 - 72.57);8	71.57 (47.42 - 72.82);11	71.44 (24.42 - 72.33);6	59.88 (48.25 - 71.50);2	10.00 (10.00 – 10.00);1
$t_{1/2}$ (h)	33.2 (124.6);3	36.8 (57.3);8	52.6 (109.5);7	65.9 (86.5);29	96.2 (60.1);5	73.8 (18.8);3	91.3 (NR);2	NC	NC

AUC_{0-t} = area under the concentration versus time curve from time zero to the last quantifiable concentration;
AUC_{0-8} = area under the concentration-time curve calculated from time 0 to time 8 hour;
AUC_{0-10} = area under the concentration-time curve calculated from time 0 to time 10 hour;
AUC_{0-24} = area under the concentration-time curve calculated from time 0 to time 24 hour;
AUC_{0-72} = area under the concentration versus time curve from 0 to 72 hr after a single dose;
PK = pharmacokinetic; C_{max} = maximum concentration for each dose; T_{max} = time to reach C_{max}; T_{last} = time to the last measured time point; NC = not calculated;
a Median (minimum, maximum)
□: SD PK Parameter 100 mg strength highlighted by the assessor

Plasma AG-221 levels generally appeared to have reached steady-state around Cycle 2, Day 1 (Day 29) across dose levels and regimens. Mean dose-normalized AG-221 C_{max} and AUC_{0-t} appeared to remain constant over the 50 to 450 mg daily dose range, suggesting dose-proportional increases in C_{max}, and AUC_{0-t} with increasing AG-221 doses also following multiple doses. The mean concentration-time profiles of AG-221 following multiple dosing showed higher concentrations than those observed after the first dose (Day -3), suggesting accumulation of AG-221 following repeated dosing.

The accumulation factor (Day -3 vs. Cycle 2 Day 1) based on AUC_{0-10} [$R(AUC_{0-10})$] and C_{max} [$R(C_{max})$] across QD dose levels (50 to 300 mg QD) ranged from 8.07 to 11.85 and from 7.63 to 10.72, respectively.

Table 3 pk Geometric Mean (Geometric CV%) Plasma Pharmacokinetic Parameters of AG-221 after Once-Daily Oral Administration (multiple dose) of AG-221 – Phase 1 – Dose Escalation and Part 1 Expansion– Cycle 2, Day 1

Plasma PK Parameters[a]	50 mg QD N=5	75 mg QD N=4	100 mg QD N=107	150 mg QD N=5	200 mg QD N=11	300 mg QD N=7	450 mg QD N=5	650 mg QD N=3
AUC_{0-8} (ng*h/mL)	43407 (106.5);5	44360 (57.2);4	83444 (48.9);102	101462 (37.7);5	108404 (53.1);11	105098 (40.9);7	181186 (21.5);5	219708 (14.6);3
AUC_{0-10} (ng*h/mL)	61226 (117.0);4	53067 (50.1);4	104824 (47.6);94	126237 (37.8);5	132718 (52.0);11	131523 (43.0);7	199749 (24.0);3	269750 (NR);2
AUC_{0-t} (ng*h/mL)	51273 (111.1);5	53067 (50.1);4	100119 (49.7);107	126237 (37.8);5	132718 (52.0);11	131523 (43.0);7	202702 (17.8);5	256155 (16.0);3
C_{max} (ng/mL)	6543 (124.9);5	6922 (64.2);4	13012 (46.5);107	15734 (38.6);5	17990 (64.0);11	18505 (42.4);7	28049 (23.4);5	35269 (10.7);3
T_{max}[b] (h)	3.02 (0.00 – 10.00);5	4.04 (1.00 - 10.08);4	1.02 (0.00 – 10.00);107	2.13 (0.70 - 9.83);5	1.02 (0.00 – 8.00);11	5.98 (0.00 - 9.95);7	4.08 (0.97 – 6.00);5	2.00 (1.95 – 3.00);3
T_{last}[b] (h)	9.92 (7.83 - 10.08);5	10.01 (8.67 - 10.08);4	9.93 (6.00 - 11.50);107	9.83 (9.83 - 10.03);5	10.00 (9.83 - 10.10);11	9.87 (9.83 – 10.00);7	9.83 (7.88 – 10.00);5	10.00 (7.40 - 10.08);3
$R(AUC_{0-10})$[c]	8.82 (48.4);3	9.76 (NR);2	11.70 (65.1);36	11.85 (51.6);5	8.62 (55.2);7	8.07 (61.2);4	NC	7.94 (NC);1
$R(C_{max})$[c]	7.73 (78.2);3	8.28 (NR);2	10.16 (58.5);42	10.72 (45.2);5	7.72 (63.5);7	7.63 (79.2);4	9.29 (NC);1	8.09 (NC);1

AUC_{0-t} = area under the concentration versus time curve from time zero to the last quantifiable concentration;
AUC_{0-8} = area under the concentration-time curve calculated from time 0 to time 8 hour;
AUC_{0-10} = area under the concentration-time curve calculated from time 0 to time 10 hour;
$R(AUC_{0-10})$ = Accumulation ratio based on AUC_{0-10};
$R(C_{max})$ = Accumulation ratio based on C_{max};
PK = pharmacokinetic; C_{max} = maximum concentration for each dose; T_{max} = time to reach C_{max}; T_{last} = time to the last measured time point; NC = not calculated;
a Median (minimum, maximum)
bR(AUC) and $R(C_{max})$ were only calculated when subjects had AUC_{0-10} and C_{max} PK parameters for both the single dose administration of AG-221 at C1D1 and the multiple dose steady-state cycle for which accumulation is being computed.
□: MD PK Parameter 100 mg strength highlighted by the assessor

An open-label, randomized, single-centre, single-dose, 2-way crossover study in healthy volunteers was conducted to assess the pharmacokinetics (PK) and safety of a single dose of AG-221 when administered orally under fasted and fed (high-fat FDA standard meal) conditions. The 90% CIs of LSM for PK parameters under fed vs. fasted conditions were above the 80.00-125.00% range for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. There was an approximate 50% increase in AUC_{0-t} and $AUC_{0-\infty}$, and a 64% increase in C_{max} when AG-221 was administered under fed conditions compared with fasted conditions.

Table 4 pk Geometric Least-squares Means Ratios and 90% Confidence Intervals of AG-221 PK Parameters Following a Single Oral Administration of 100 mg AG-221 Under Fasted and Fed Conditions (Food-Effect PK Analysis Set; N=28)

Parameter	Geometric LSM[a]		% Ratio of LSM[b] (90% CI)	Intra-subject CV%
	Treatment B (Fed)	Treatment A (Fasted)		
AUC_t	80.0	53.5	150 (135, 166)	23.3
AUC_∞	80.3	53.8	149 (135, 166)	23.1
C_{max}	1.35	0.827	164 (144, 186)	29.1

ANOVA = analysis of variance; AUC = area under the plasma concentration time curve; AUC_∞ = AUC from zero to infinity; AUC_t = AUC from zero to the time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed concentration in plasma; CV% = coefficient of variation; LSM = least-squares means
[a] Geometric LSM are the LSM from ANOVA presented following back transformation to the original scale. The 90% CIs are presented following back transformation to the original scale.
[b] Ratio of Fed (Treatment B) / Fasted (Treatment A)

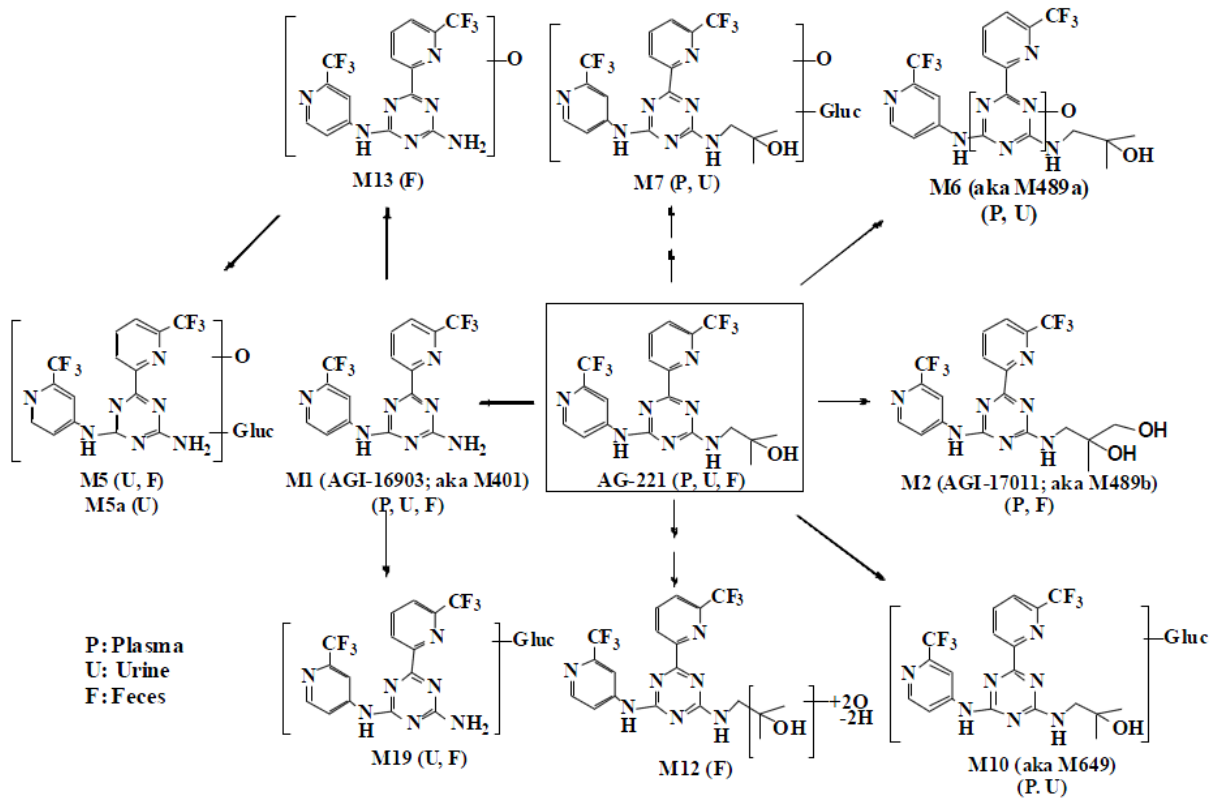
The effect of food and fasting on AG-221 exposure was further evaluated in the Phase 1 portion of Study AG221-C-001. Specifically, AG-221 dosing without food restrictions was conducted in 4 subjects at doses of 200 mg and 300 mg (F3) as a single dose at Day -3 and then for 15 days of treatment starting at C1D1 through C1D15. As of 01 Sep 2017, there were 2 to 4 subjects in separate cohorts who received 200 mg and 300 mg doses with food through Cycle 1 Day 15. There were large variations

in AG-221 exposure at the 200 mg and 300 mg doses and no obvious food effect was observed when AG- 221 exposure under fed conditions (n = 2-4) was compared with that under fasted condition (n = 3-10).

Following oral dosing, AG-221 related radioactivity is rapidly absorbed with peak blood and plasma concentrations reached between 1 and 2 hours then concentrations declined over time. Overall mean recovery of total radioactivity (TRA) was approximately 82%, with approximately 73.0% and 8.4% of TRA recovered in faeces and urine, respectively, during the 504-hour postdose collection period. These data indicate that elimination of TRA was primarily via faecal excretion.

During the 240-hour postdose period (the time frame during which metabolite profiling was performed), excreted metabolites and unchanged AG-221 accounted for greater than 47.1 % and 24.9 % of the administered dose, respectively. Among the 47.1 % of dose for excreted metabolites over 240-hour postdose period, faecal excretion of metabolites accounted for 39.9 % of the administered dose. The results suggested AG-221 appears to be mainly cleared by metabolism, with the resulting metabolites eliminated primarily in the faeces.

Figure 1 pk Proposed Metabolic Pathway in Humans



Source: Clinical Study report AG-221-CP-002; Figure 4 pg. 41

As illustrated above, AG-221 is metabolized by multiple pathways including N-dealkylation, oxidation, direct glucuronidation and combinations of these pathways. AG-221 and five metabolites were detected in human plasma. The parent AG-221 was the predominant radioactive component in plasma in healthy subjects who received a single oral dose of [^{14}C]-AG-221 (100 mg) at all time points. The metabolite M1 (N-dealkylation) was the most prominent metabolite. Based on exposure (AUC_{0-24}), AG-221 and M1 accounted for 89% and 10% of circulating total radioactivity (TRA) exposure, respectively,

while the oxidation metabolites M2 (AGI-17011) and M6 were minor metabolites in plasma, representing 0.3% and 0.06% of TRA, respectively. Metabolites M7 (oxidation and glucuronidation) and M10 (direct glucuronidation) were also detected in plasma as minor metabolites, but their exposures were not calculated due to the low concentrations.

A study in subjects with renal impairment has not been conducted with AG-221, in the clinical study AG221-C-001, subjects with creatinine clearance ≤ 40 mL/min were excluded. In the combined Phase 1/2 population, 22 (6.7%) subjects had a baseline creatinine clearance of < 45 mL/min, 46 (13.9%) subjects had a baseline creatinine clearance of 45 to < 60 mL/min, and 257 (77.9%) subjects had a baseline creatinine clearance of ≥ 60 mL/min.
A study in subjects with hepatic impairment has also not been conducted with AG-221. Study CC-90007-CP-003 to assess PK in subjects with moderate and severe hepatic impairment has been initiated in the US.

No formal clinical drug interaction studies have been performed so far. Enasidenib metabolism was examined using human liver microsomes, recombinant cytochrome (CYP) and uridine diphosphate glucuronosyltransferase (UGT) enzymes (Report AG221-N-003-R1; Report AG221-N-036-R1). According to the Applicant´s Response to the CHMP Day 120 LoQ, a drug-drug interaction study in approximately 42 subjects with AML harboring an IDH2 mutation to estimate the effects of enasidenib at steady state on the measured plasma concentrations (AUC_{0-24} and C_{max}) of single doses of the selected test drugs started enrolling in Oct 2018.

3.3.2. Pharmacodynamics

Primary pharmacodynamics

In clinical Phase 1/2 study AG-221-C-001 several analyses were performed on PD parameters 2-HG, IDH2 mutation (mIDH2) variant allele frequency (VAF) and co-mutational burden as exploratory objectives. Blood samples collected for PK assessments were also used for assessment of PD parameters. The potential relationship between plasma levels of enasidenib and plasma, urine, and bone marrow 2-HG levels was explored with descriptive and graphical methods.

The bioanalytical method determined racemic total 2-HG, an enantioselective to analyse the oncometabolite D-2-HG was not utilised.

Dividing patients into daily dose groups suggested nearly complete **2-HG suppression**. However, separation by IDH2 mutation (R140 n=107, R172 n=34) indicated near maximal suppression in the majority of R140 subjects at 100 mg, with no additional inhibition observed at higher doses. In contrast, in R172 subjects, there was no clear dose-dependent inhibition observed when similarly analysed by three dose groups (Figure pd1). An analysis of 2-HG at C4D1 was performed. In R172 subjects, there was no clear pattern of 2-HG suppression at this later time point (Figure pd2). There was a clear difference between R140 and R172 groups in that the extent of 2-HG suppression was lower in R172 versus R140 subjects. This may reflect the drug binding affinity and/or catalytic activity between the variants of the mutant IDH2 enzyme.

Figure pd1 Cycle 2 D1: Maximum % suppression of 2-HG vs. enasidenib AUC_{0-10} by IDH2 mutation status and exposure – combined Phase 1

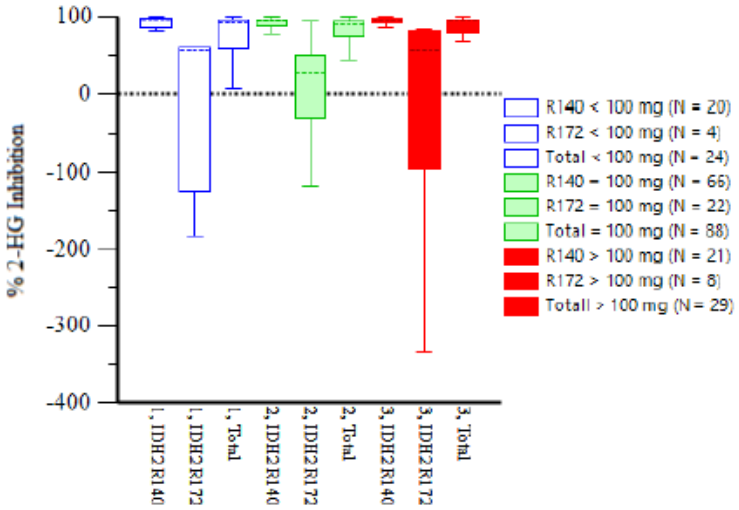
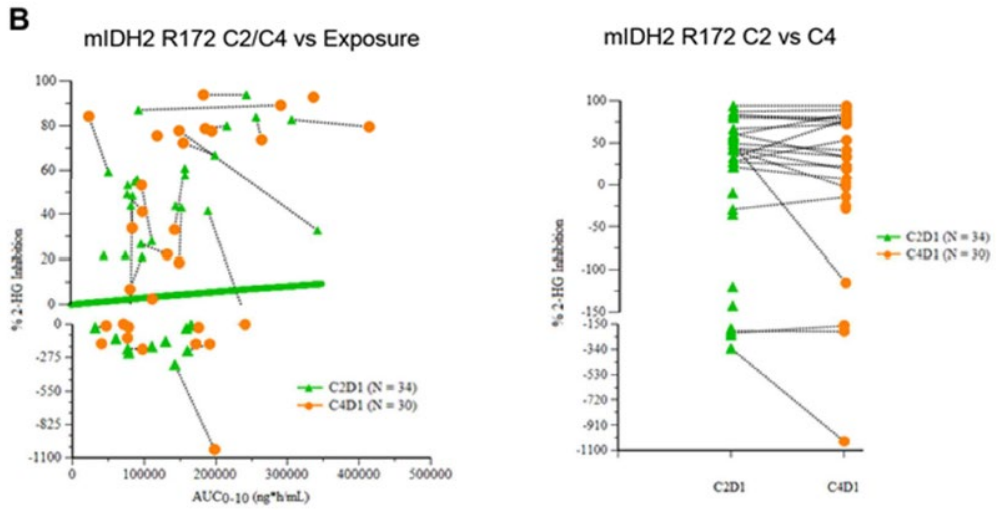
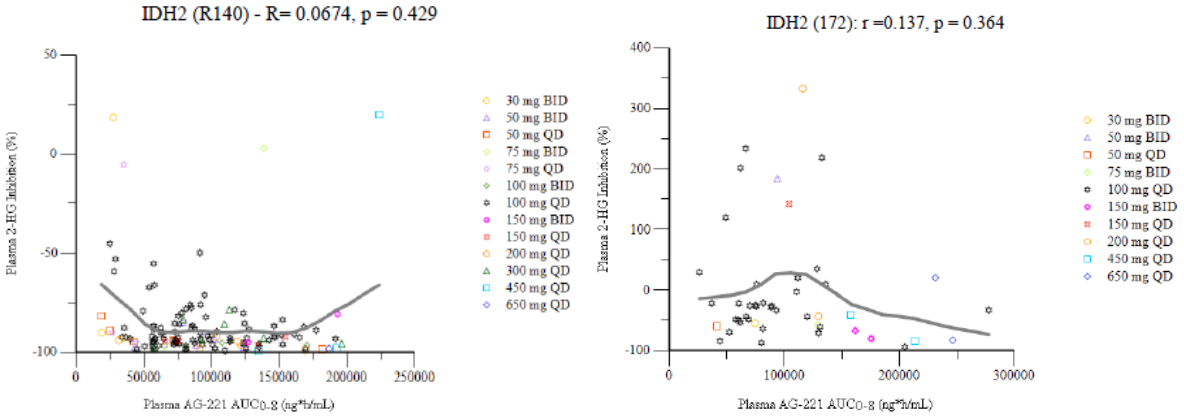


Figure pd2 Cycle 4 D1: Maximum % suppression of 2-HG vs. enasidenib AUC_{0-10} by IDH2 mutation status and exposure



Over the enasidenib 50-600 mg QD dose levels, 2-HG generally decreased >75% from BL for subjects with mutations in IDH2 R140 (n=140) and there were minimal additional decreases in plasma 2-HG levels with increasing AG-221 exposure. No trends in plasma 2-HG levels change from BL were observed for subjects with mutations in IDH2 R172 (n=46) (Figure pd3).

Figure pd3 C2D1 Max. % suppression of 2-HG vs. enasidenib AUC_{0-10} – Phase 1/2

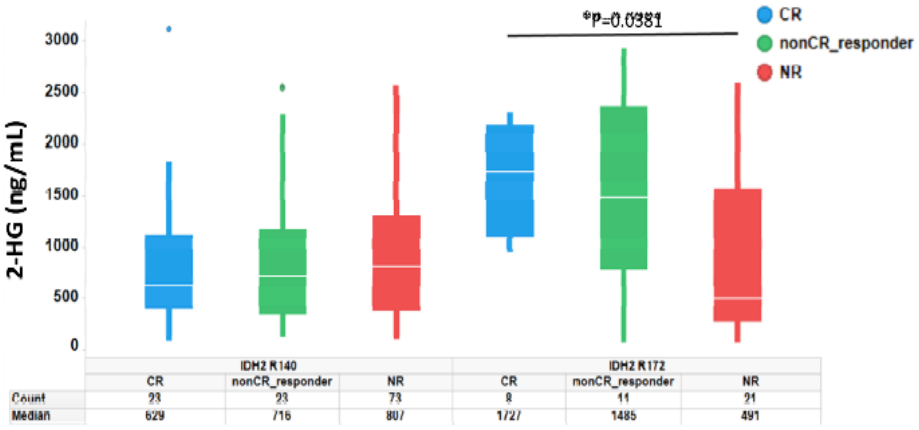


The time to maximum decrease of 2-HG from baseline (Tmin) was observed between 23.9 to 48.7 h, with some exceptions.

Baseline plasma levels of 2-HG were measured by mass spectrometry in 227 r/r AML mIDH2 patients (phase 1 n = 123; phase 2 n = 104). At baseline, R172 mIDH2 patients had higher levels of 2-HG compared to R140 mIDH2 patients (median 1102 ng/mL *vs.* 800 ng/mL, p = 0.0099).

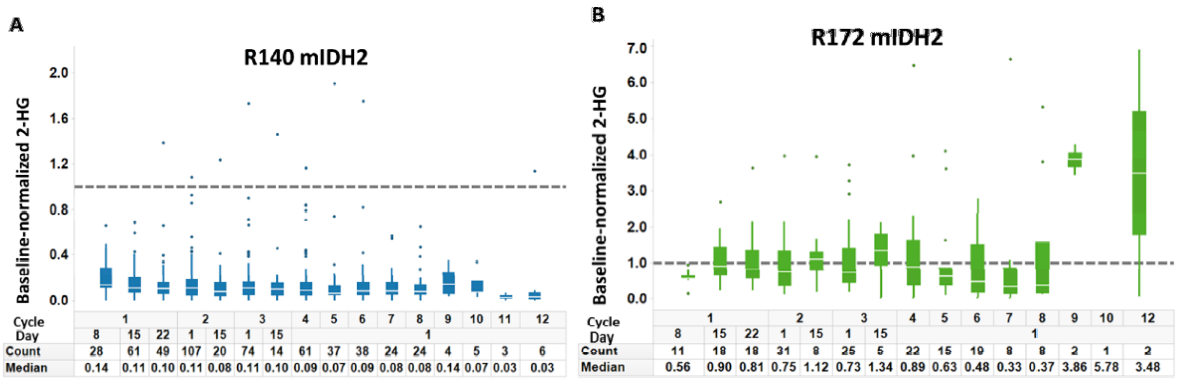
Correlation between baseline 2-HG levels and clinical response was evaluated in 159 r/r AML patients (n = 65 phase 1 patients, n = 94 phase 2 patients) treated with 100 mg/day enasidenib. Higher levels of BL 2-HG were seen in R172 mIDH2 patients that achieved CR compared to patients with non-response (NR) (1727 *vs*. 491 ng/mL; p = 0.0381).

Figure pd4 Phase 1/2: Baseline plasma 2-HG levels in r/r AML patient population



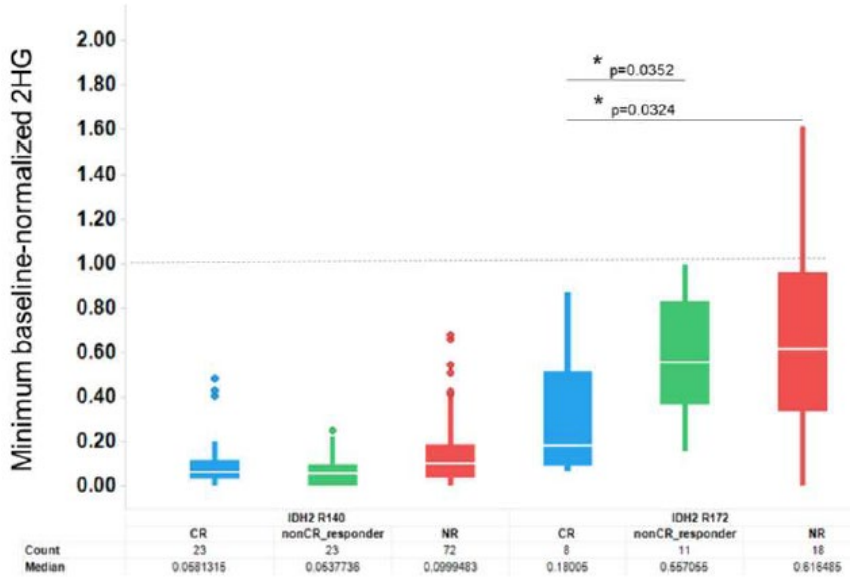
During treatment, median baseline-normalized 2-HG reductions approached or exceeded 10-fold within the first treatment cycle in R140 mIDH2 subjects and were sustained throughout the first year of treatment (median -92.9%). In contrast, no clear trend in median 2-HG reduction over time was observed in R172 mIDH2 subjects (median -47.4%) (p = 0.0004).

Figure pd5 Phase 1/2: plasma 2-HG levels during treatment with 100 mg/day enasidenib



However, no correlation between 2-HG reduction and clinical response was seen in R140 mIDH2 patients whereas a statistically significant association in reduction of 2-HG was observed in R172 mIDH2 CR compared with non-CR response and NR groups (82.0%, 44.3%, and 38.4% reduction in CR, non-CR response, and NR groups, respectively).

Figure pd6 Phase 1/2: Minimum BL-normalized 2-HG levels during treatment with 100 mg/day enasidenib



Levels of 2-HG in PB plasma correlated with levels in bone marrow and in urine at baseline and during treatment.

IDH2 mutant allelic burden was analysed and the potential correlation between mIDH2 variant allele frequencies (%VAF) and clinical response was investigated in r/r AML patients enrolled in Phase 1. VAF thresholds for detection by digital droplet PCR (ddPCR) were 0.02% (R172) - 0.04% (R140).

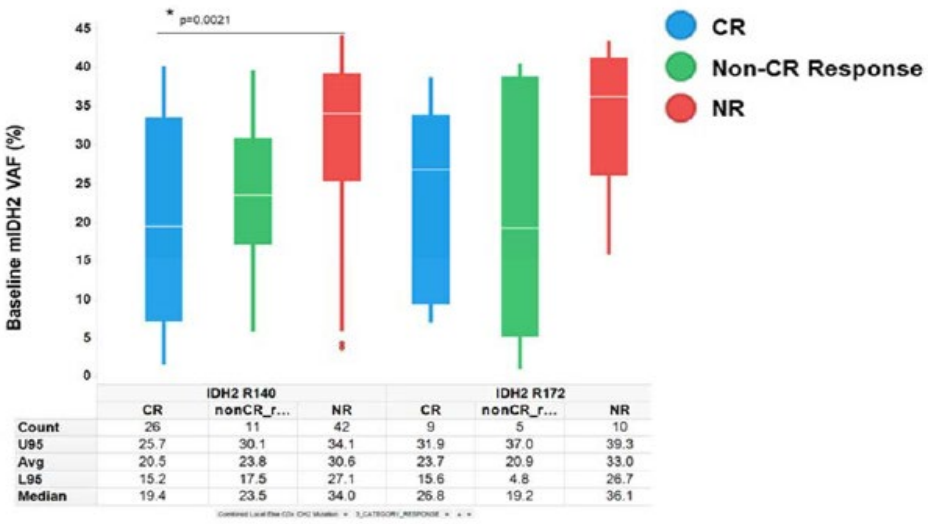
Bone marrow mononuclear cells or PBMCs were isolated from patients at BL or during treatment. IDH2 VAF at BL and extent of change in VAF during treatment were evaluated in association with clinical response (modified IWG response criteria).

VAF at BL were highly variable among patients, ranging from just above the limit of detection for each assay to clonal (i.e., VAF of ~0.5 = 50% as IDH2 is known to be a heterozygous mutation), suggesting a non-uniform disease burden in the enrolled patients.

A combined analysis of efficacy-evaluable r/r AML patients from phase 1 (N = 20) and phase 2 (N = 83) trials on 100 mg enasidenib was performed. There was no statistically significant difference in mean BL mIDH2 VAF between R140 and R172 mIDH2 patients (26.3% vs. 27.0%, n = 79 and 24, resp.).

A statistically significant difference in mean baseline VAF was detected in R140 mIDH2 that achieved CR vs. NR patients (20.5% vs. 30.6%). However, it should be noted that baseline mIDH2 VAF varied widely (from 1.6% to 40.1%) in R140 patients who achieved CR. No statistically significant difference in mIDH2 VAF was observed in IDH2 R172 patients stratified by clinical response.

Figure pd7 IDH2 VAF at BL by best response in phase 1/2 r/r AML patients on 100 mg enasidenib

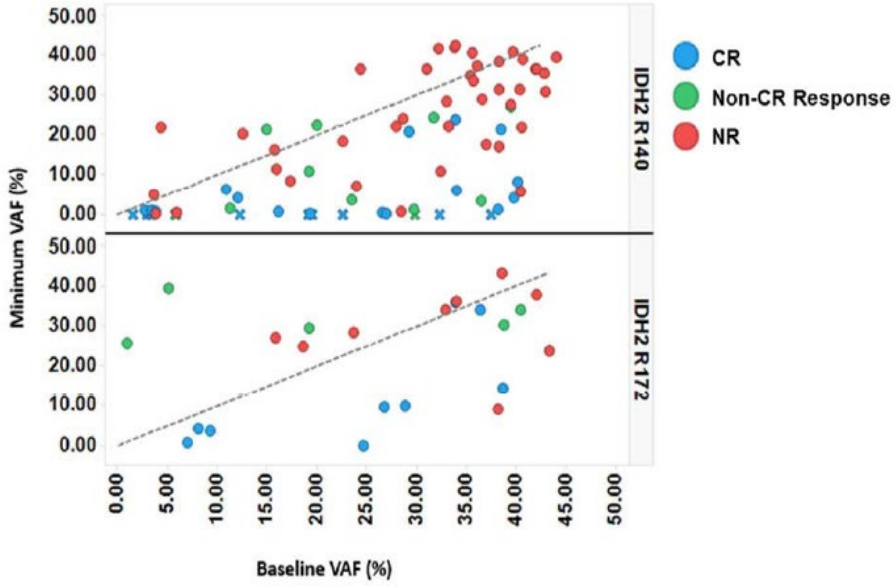


	IDH2 R140			IDH2 R172		
	CR	nonCR_r...	NR	CR	nonCR_r...	NR
Count	26	11	42	9	5	10
U95	25.7	30.1	34.1	31.9	37.0	39.3
Avg	20.5	23.8	30.6	23.7	20.9	33.0
L95	15.2	17.5	27.1	15.6	4.8	26.7
Median	19.4	23.5	34.0	26.8	19.2	36.1

Reductions of the median BL-normalized VAF down to <10% were seen in R140 mIDH2 patients over time. In contrast, median BL-normalized VAF in R172 mIDH2 patients did not fall below 90% at any timepoint assessed.

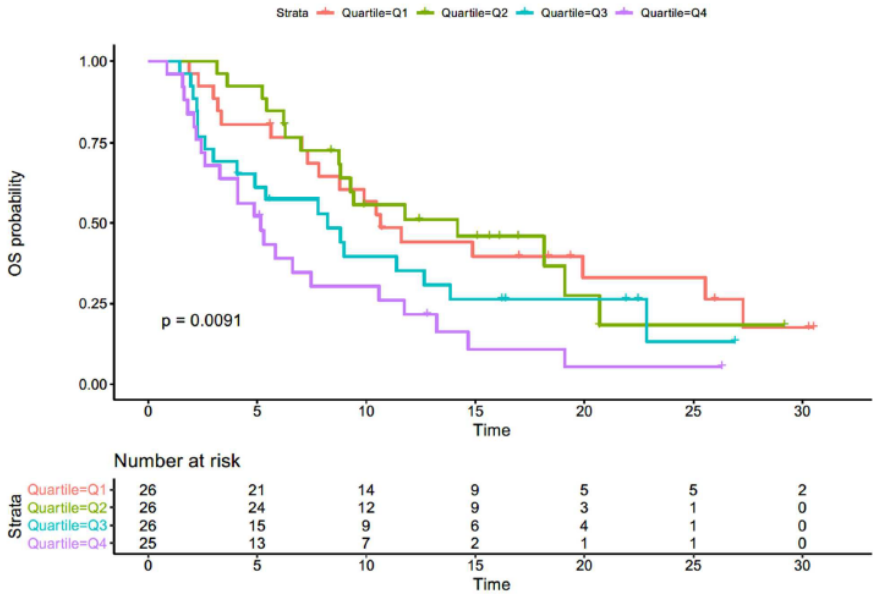
Twelve patients (11.9%) achieved molecular CR, defined as mIDH2 VAF below the limit of detection (0.02%-0.04%) at one or more timepoint during treatment, and all achieved a clinical response (10 CR, 1 CRp, and 1 PR). While clinical responses were observed both in patients with and without reductions in mIDH2 VAF, clinical response rates were significantly higher (p = 0.0003) in patients with VAF reductions below the limit of detection. No patients with R172 mIDH2 in the cohort achieved VAF reductions below the limit of detection. 2/23 patients with R172 mIDH2 achieved VAF <2% (log <-1.7), these were also accompanied by CR. Longitudinal data for VAF are available for only 1 patient showing that VAF dropped below LLOQ under enasidenib treatment and increases again, displaying relapse.

Figure pd8 Changes of IDH2 VAF in phase 1/2 r/r AML patients on 100 mg enasidenib by clinical response



Median OS in subgroups defined by quartiles of baseline mIDH2 VAF of both mutants together were 10.66 months in Q1, 14.18 months in Q2, 8.22 months in Q3, and 5.16 in Q4 (for Q4 *vs.* Q1: HR 2.45 [1.30, 4.63]; Figure pd8a).

Figure pd8a OS of patient subgroups by quartiles of baseline mIDH2 VAF

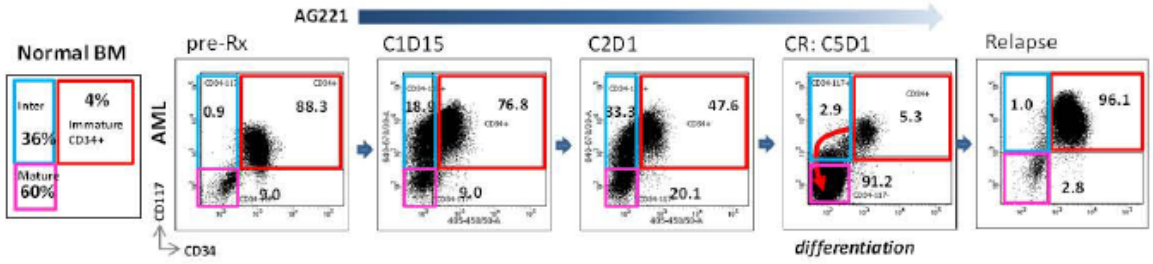


Functional and genomic assessment of hematopoietic cell populations in patients treated with enasidenib was performed. Samples from 24 individual patients enrolled in Phase 1 were used for experiments. Multiple types of experiments were conducted using the same samples from 2 patients ([R172] and [R140]).

Patients who achieved CR following treatment with enasidenib demonstrated near normalization of the ratio of immature progenitor/precursor cells to mature granulocyte-macrophage/monocyte (GM) cells (N = 4). Furthermore, significant proportion of these mature GM cells harboured the IDH2 mutation at

CR. In contrast, SD/PD patients did not achieve normalization of the immature: mature cells ratio. At relapse, re-expansion of immature progenitor/ precursor cells was observed (N = 2).

Figure pd9 Representative example of longitudinal analysis of patient bone marrow mononuclear cells by hematopoietic stem-progenitor-precursor-mature flow panel



AML = acute myeloid leukemia; BM = bone marrow; BMMC = bone marrow mononuclear cells; C = cycle; D = day; HSPPM = hematopoietic stem-progenitor-precursor-mature; pre = precursor; Inter = intermediate.
Representative example of longitudinal analysis of patient BMMCs by HSPPM FACS: numbers in FACS plots refer to size of population as % of lineage-negative BMMCs. The expected percentages of stem/progenitor; precursors and mature cells in normal BM are shown on the left.

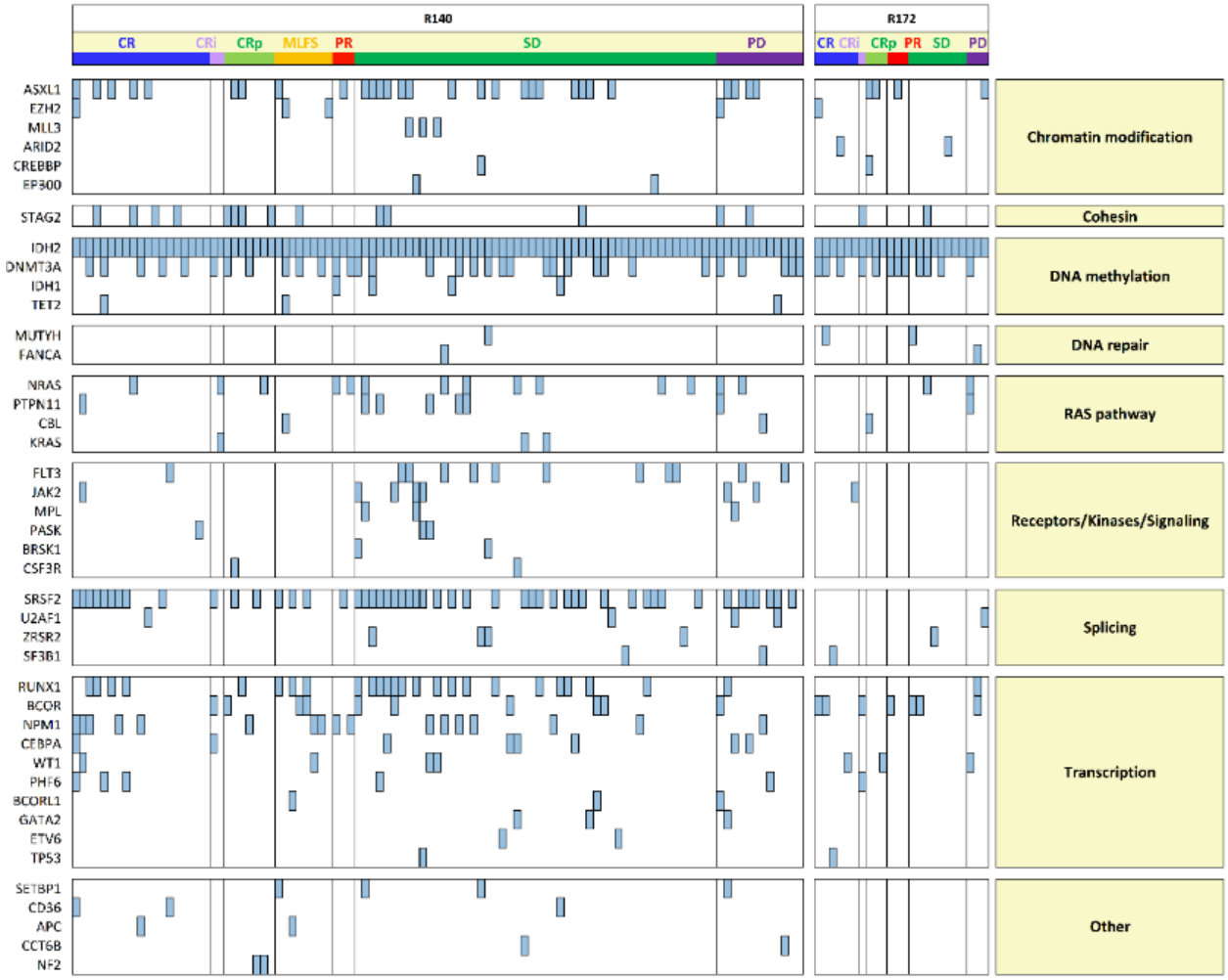
It is concluded that these data are consistent with a mechanism of action of enasidenib whereby inhibition of mutant IDH2 enzyme results in differentiation of the immature leukemic blasts into functional and mature GM cells that retain the IDH2 mutation.

Gene mutation profiles in bone marrow mononuclear cells of patients at BL were generated and potential correlation of gene mutations with clinical response to enasidenib was evaluated. The threshold for detection of co-mutations by NGS was ~1%.

In phase 1, 98% of samples contained an additional mutation and 17 co-occurring mutated genes were found at a frequency ≥5%. The prevalence of mutations differed from those reported in *de novo* AML, including increased frequency in poor prognostic genes DNMT3A, ASXL1, and RUNX1 and decreased frequency of mutations in good prognostic genes, including NPM1 and CEBPA. Co-mutational heterogeneity appeared to be significantly higher in R140 patients with 60 different mutated genes versus 24 identified in R172 mIDH2 patients.

In phase 2, 14 additional genes were mutated at a frequency ≥5%. The genes most frequently mutated were SRSF2 (42.0%), DNMT3A (38.5%), ASXL1 (27.0%), RUNX1 (20.1%), NRAS (14.4%), and BCOR (13.8%).

Figure pd10 Mutation Profiles by IDH2 Mutation at BL in r/r AML patients: on 100mg/d (upper), total population (lower)

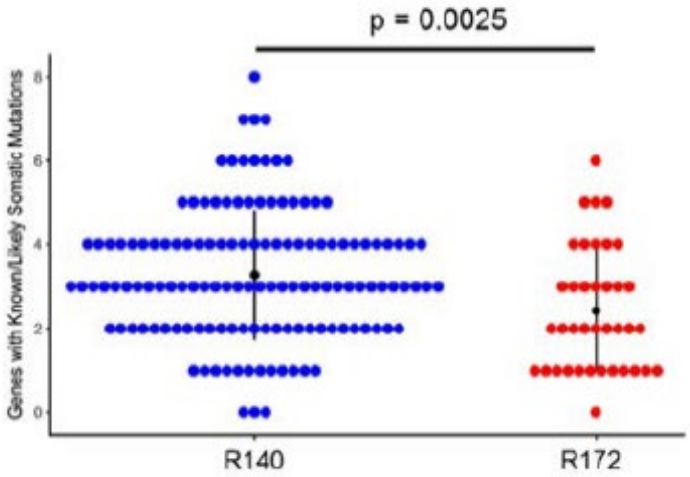


Gene	IDH2-R140 (n = 132)	IDH2-R172 (n = 38)	P-value[a]	Preference
	Mutated n (%)	Mutated n (%)		
SRSF2	72 (54.5)	1 (2.6)	< 0.0001	R140
NPM1	21 (15.9)	0 (0)	0.0046	R140
RUNX1	32 (24.2)	2 (5.3)	0.0102	R140
DNMT3A	45 (34.1)	22 (57.9)	0.0136	R172
FLT3	16 (12.1)	0 (0)	0.0241	R140
BCOR	14 (10.6)	10 (26.3)	0.0309	R172
ARID2[b]	0 (0)	2 (5.3)	0.0489	R172

Only mutated genes occurring in 2 or more patients are shown.

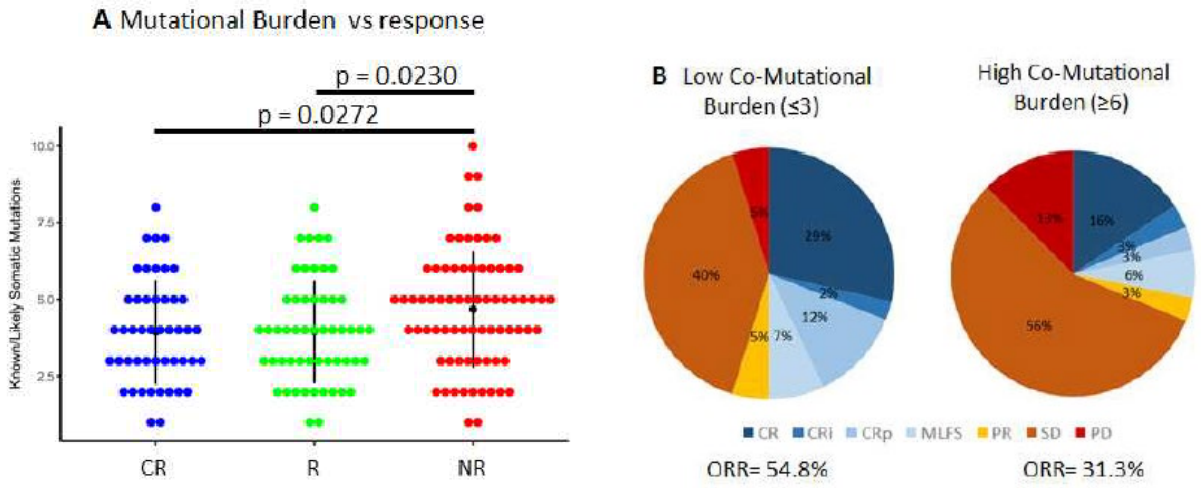
Total co-mutational burden was significantly lower in R172 mIDH2 patients *vs.* R140 mIDH2 patients, with 2.4 *vs*. 3.3 co-mutated genes per patient, respectively.

Figure pd11 Co-mutational burden vs. IDH2 in phase 2

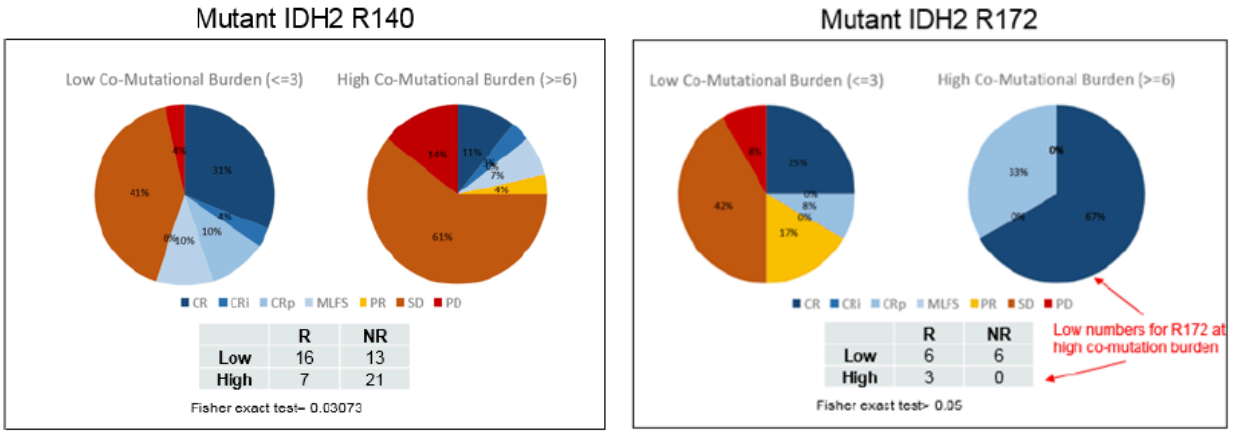


Analysis of the number of mutations by response category showed that patients with OR had statistically significant fewer co-occurring mutations than NR patients. When divided by number of co-mutations, a lower ORR was observed in ≥ 6 *vs.* ≤ 3 co-mutations.

Figure pd12 Analysis of mutational burden and response to 100 mg/day enasidenib



C Separated for mutant isoforms



Association of clinical response by co-mutational status was analysed (Table pd1).

Table pd1 Association of clinical response by mutation status for r/r AML patients (upper) and under 100mg/d treatment (lower)

	n[a]	R140 (n)[a]	R172 (n)[a]	ORR	ORR, OR	ORR, P-value	CR	CR, OR	CR, P-value
Gene									
NRAS	25	18	6	0.24	0.376	0.0502	0.12	0.22	0.0115
Pathway									
Receptors/Kinases/Signaling	47	41	6	0.255	0.359	0.006	0.191	0.353	0.0116
RAS Pathway	37	28	7	0.297	0.497	0.0924	.189	0.37	0.0314

	n[a]	R140 (n)[a]	R172 (n)[a]	ORR	ORR, OR	ORR, P-value	CR	CR, OR	CR, P-value
Gene									
STAG2	16	14	2	0.625	2.636	0.1027	0.625	3.333	0.0295
FLT3	12	12	0	0.083	0.11	0.014	0.083	0.136	0.0317
Pathway									
Receptors/Kinases/Signaling	36	33	3	0.222	0.292	0.0054	0.167	0.244	0.0039
Cohesin	16	14	2	0.625	2.636	0.1027	0.625	3.333	0.0295
Splicing	62	58	3	0.29	0.351	0.0067	0.274	0.441	0.0427

Secondary pharmacodynamics

In vitro

Enasidenib and its metabolite AGI-16903 were evaluated *in vitro* for their potential to inhibit binding and enzymatic activity in a panel of receptors, ion channels, transporters, and enzymes and kinases. For enasidenib, significant inhibition ≥50% were noted for adenosine A_1 (96%), adenosine A_{2A} (63%), adenosine transporter (87%), serotonin $5HT_4$ (69%), serotonin $5HT_6$ (69%), and phosphodiesterase ($PDE4_{A1A}$; 50%)

Cardiac safety

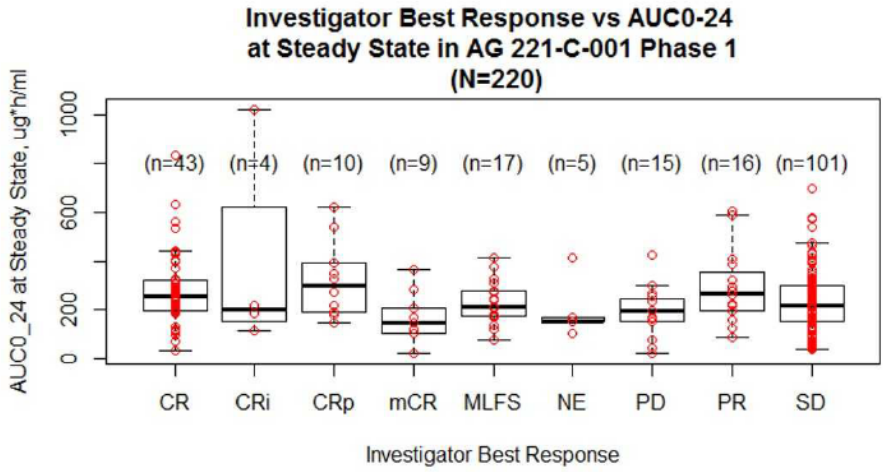
With regard to cardiac safety, the exposure-response analysis from ECG results obtained from the main study AG221-C-001, confirmed the results from PK studies in HV, that the potential for significant concerns regarding QTc prolongation with enasidenib is minimal.

Exposure-response relationship

A comparison of the steady state exposure between the 2 mutation types (R140Q and R172K) indicated that the average steady state AUC_{0-24} was similar.

The exposure-response relationship for the clinical response was explored in 315 subjects who received at least one dose and had plasma exposure data after the first dose. The main exposure metrics were AUC_{0-24} at steady state simulated/estimated from final PPK model. Figure pd13 shows that there is no apparent relationship between systemic enasidenib exposure levels and the clinical best responses, in the range of 50 mg to 650 mg/daily.

Figure pd13 Relationship between $AUC_{0-24,ss}$ and Inv-assessed best responses in Phase 1



3.3.3. Discussion on clinical pharmacology

Bio-Analytical Methods

The quantitative analysis of Enasidenib free base (laboratory codes: AG-221, CC-90007 free base, and AGI-12910) and its metabolite (M1) AGI-16903, was accomplished by HPLC-MS/MS. Furthermore, to better understand the relationship between 2-hydroxyglutarate (2-HG) levels and response to enasidenib (AG-221, CC-90007; henceforth referred to as AG-221), an analysis of total 2-HG levels in patients with relapsed/refractory acute myeloid leukemia (R/R AML) enrolled in AG221-C-001 and the potential correlation with clinical response was performed. Results are reported separately for patients in phase 1 and phase 1/2 cohorts. Total 2-HG concentration was determined by qualified liquid chromatography tandem mass spectrometry

However, the analytical method for the determination of 2-hydroxyglutarate concentration levels in study subjects is qualified but not fully validated; see PD discussion below. The bioanalytical test method for determination of enasidenib and its metabolite in urine and feces is a qualified method, only not fully validated according to EMA regulations. This is acceptable in context with the explorative objective of this method /study to support the metabolite profiling in human matrices (i.e., urine, blood, plasma, and feces) as well as the quantitation of [14C]-AG-221 (for support of absolute bioavailability experiments) in human plasma by HPLC and AMS.

The bioanalytical method for the determination of 4ß-hydroxycholesterol and cholesterol in human plasma, (that was one of the objectives of Study AG221-C-001 to monitor plasma cholesterol and 4beta-hydroxy (4β-OH)-cholesterol levels as a potential CYP3A4 induction marker), lacks proof of long term stability covering the storage time of the study samples from date of collection until last date of analysis. This needs to be addressed by the applicant.

Pharmacokinetics

The clinical development programme included clinical studies with overall 4 formulations for AG-221 (F1A, F1B, F2 and F3). The tablet formulation F3 was used in studies characterising the PK in healthy subjects (AG-221-CP-001 and AG-221-CP-002) and in the pivotal study AG221-C-001

(expansion phase in relapsed/refractory AML). Formulation F3 is the intended to-be-marketed (commercial use) formulation and the one currently marketed in the United States.

With regard to the similarity of the different formulations used in the clinical development, no *in vivo* bioequivalence study was conducted. The plasma exposures of AG-221 by different formulations were, however, compared in a detailed metaanalysis, pooling PK data from both healthy subjects and subjects with advanced hematologic malignancies. PK characteristics (rate and extent) were shown to be overall similar.

Following single oral doses, AG-221 was rapidly absorbed; the absolute bioavailability after 100 mg oral dose of enasidenib was found to be approximately 57 %. The area under concentration time curve (AUC) of enasidenib increases in an approximately dose proportional manner from 50 mg (0.5 times recommended dosage) to 450 mg (4.5 times recommended dosage) daily dose. After multiple dosing, AG-221 showed a long plasma half-life with 9- to 11-fold accumulation in subjects with advanced hematologic malignancies according to combined analysis of the Phase 1 and Phase 2.

With regard to the stated peak plasma concentration (C_{max}) after single and multiple doses of 100 mg AG221, the SmPC was amended in response to the ChMP D120 LoQ. As proposed, the Applicant amended the SmPC to reflect the combined Phase 1 and Phase 2 data of the AG221-C-001 study after a single 100 mg QD dose.

Results after administration of 100 mg of the F2 formulation tablets with food in healthy subjects showed an increase of the overall extent (AUC) of absorption by ~50% compared to administration under fasting conditions. The effects of concomitant food intake on the rate of absorption (C_{max}) were comparable (increase by ~64%). Median time to reach C_{max} (median T_{max}) in healthy subjects was 4 hours under fasting as well as under fed conditions.

The effect of food and fasting on AG-221 exposure was further evaluated in the Phase 1 portion of Study AG221-C-001. Specifically, AG-221 dosing without food restrictions was conducted in 4 subjects at doses of 200 mg and 300 mg as a single dose at Day -3 and then for 15 days of treatment starting at C1D1 through C1D15. As of 01 Sep 2017, there were 2 to 4 subjects in separate cohorts who received 200 mg and 300 mg doses with food through Cycle 1 Day 15. There were large variations in AG-221 exposure at the 200 mg and 300 mg doses and no obvious food effect was observed when AG-221 exposure under fed conditions (n = 2-4) was compared with that under fasted condition (n = 3-10). The applicant concludes that no obvious food effect was observed when AG- 221 exposure under fed conditions was compared with that under fasted condition in study AG221-C-001 after single and multiple doses, which is acknowledged. However, based on the very variable results in such a small number of patients, the provided comparison is regarded not to be very sensitive to further reveal possible food effects.
In summary, the statement in the currently proposed SmPC: "There was an approximate 50 % increase in AUC_{0-t} and $AUC_{0-\infty,}$ and a 64 % increase in C_{max} when enasidenib (single 100 mg dose) was administered under fed conditions compared with fasted conditions." is in line with the submitted data and therefore adequately justified. Based on the overall data available in healthy subjects and patients with advanced hematologic malignancies with an IDH2 mutation, it can also be agreed on with the Applicant that the possible small increase in AG-221 exposure seen with food ingestion is not likely to affect its efficacy and safety.

As twice-daily and once-daily AG-221 dosing showed generally comparable exposure at the same total daily dose, the QD dosing proposed in the currently proposed SmPC, which was the dosing regimen also used in the Phase 2 part of Study AG-221-C-001, seems adequately justified.

The proposed SmPC was updated to reflect the original volume of distribution of 55.8 L (CV% 29) following an IV dose of 0.1 mg in healthy volunteers as also stated in the US prescribing label. As the

unit for volume of distribution given in section 5.2 of the SmPC should be L/kg as recommended by the Guideline on SmPC, the SmPC was further amended.

Enasidenib is eliminated by the liver, mainly through metabolism. After administration of radiolabelled drug, the majority of radioactivity was recovered in feces (73.0%) with a small fraction of the dose recovered in urine (8.4%). Because the bioavailability is about 57%, unchanged drug found in the faeces is most probably unabsorbed drug. Therefore, there is probably no significant biliary excretion. Excretion of parent drug in urine was minimal, representing 0.3% of the administered dose. Metabolites identified in the urine represented each less than 1% of the administered dose. Unchanged drug accounted for 24.6% and metabolites for 39.9% of the fecal radioactivity recovered during the 240-hour post dose period.

AG-221 is metabolized by multiple pathways including N-dealkylation, oxidation, direct glucuronidation and combinations of these pathways. AG-221 and five metabolites were detected in human plasma. The parent AG-221 was the predominant radioactive component in plasma in healthy subjects who received a single oral dose of [^{14}C]-AG-221 (100 mg) at all time points.
The metabolite M1 (N-dealkylation) was the most prominent metabolite. Based on exposure (AUC_{0-24}), AG-221 and M1 accounted for 89% and 10% of circulating total radioactivity (TRA) exposure. Information provided in the SmPC are in line with the study results and acceptable.

Minor plasma metabolites were M2 (AGI-17011), M6, M7 and M10. Metabolic pathways of in humans included N-dealkylation, oxidation, direct glucuronidation, and combinations of these pathways. N-Dealkylation was the most prominent metabolic pathway in humans. The PK of the main metabolite, M1, have been characterised after single dosing. The metabolite is formed rather slowly and its $t_{1/2}$ is similar to that of the parent drug after a single dose. There are indications that the clearance of the metabolite decreases after multiple dosing, as it occurs for the parent drug. The hepatic clearance of enasidenib is low and decreases following repeated administration. After a single oral dose administered to HS, CL/F was 2.39 and $t_{1/2}$ was 29.0 h. As PK samples were not collected beyond 72 hours in patients, the elimination phase in patients was not fully characterised. Therefore $t_{1/2}$ was not calculated. Based on the Population PK analysis, in patients, the average CL/F and terminal half-life after multiple doses were estimated to be 0.70 L/hr and 190 hours, respectively. This decrease in the drug clearance may be due to auto-inhibition of drug metabolism. Based on the estimated PopPK $t_{1/2}$ value, steady-state was not fully reached by Cycle 2, Day 1.

Based on the estimated PopPK t1/2 value, it seemed that steady-state would not be fully reached by Cycle 2, Day 1 and the Applicant was asked at D80 of the procedure to further discuss this point and, if possibly, provide concentration data collected after a longer time of administration than 28 days (i.e. Day 1, Cycle 2). The Applicant responded stating that as per the population pharmacokinetics (PK) analysis (Report AG-221-MPK-001) the CL/F of 0.70 L/hr was estimated from both single- and multiple-dose PK in patients using trough concentration data collected for up to 8 cycles and that enasidenib has shown different PK profiles in patients compared with healthy subjects (~3.5-fold difference in apparent clearance). Enasidenib trough concentrations were collected during repeated dosing, including on Cycle 2 Day 1. It was stated that based on this information there is no obvious evidence of time-dependent enasidenib PK (auto-inhibition) and that the linear PK model (constant clearance model) used in the population PK analyses adequately characterized the enasidenib concentration profile with appropriate precision; the observed significant enasidenib drug accumulation can be predicted from enasidenib's linear PK.
The Applicant´s response was regarded acceptable and it can be agreed that data indicate that CL/F is much lower in patients than in healthy subjects. Further, the trough level values provided by the Applicant show that after Cycle 2 the enasidenib trough concentration reached a plateau with limited fluctuation i.e. steady-state was fully reached.

Pharmacokinetics in special populations have been discussed by the Applicant. In the presented population PK analysis, no clinically meaningful effect of the PK of enasidenib was observed for the following covariates: gender, age (19 years to 100 years), race (White, Black or Asian), mild hepatic impairment [defined as total bilirubin ≤ upper limit of normal (ULN) and aspartate transaminase (AST) > ULN or total bilirubin 1 to 1.5 times ULN and any AST], and renal impairment ((defined by Cockcroft Gault formula as: mild renal impairment: 60 ml/min ≤ CRCL < 90 ml/min and moderate renal impairment: 30 ml/min ≤ CRCL< 60 ml/min). But in the exposure-safety analysis, higher total bilirubin levels were found to be associated with high drug exposure (according to the amendment of the popPK and ER report). The Applicant stated that the popPk model will be revised when Phase 3 data are available. It is expected that the fit to the data including variability will be improved and covariate analyses redone with the revised model.

A study in subjects with renal impairment has not been conducted with AG-221; in the clinical study AG221-C-001, subjects with creatinine clearance ≤ 40 mL/min were excluded. In the combined Phase 1/2 population, 26 (7.5%) subjects had a baseline creatinine clearance of < 45 mL/min, 54 (15.7%) subjects had a baseline creatinine clearance of 45 to < 60 mL/min, and 264 (76.5%) subjects had a baseline creatinine clearance of ≥ 60 mL/min. A population PK analysis based on the cumulative data suggested creatinine clearance is not a significant covariate on AG-221 plasma exposure. According to the Applicant, based on that population pharmacokinetic analysis, no dose adjustments are required for patients with renal impairment (creatinine clearance [CrCl] > 30 ml/min) and there is not enough data to draw a conclusion for patients with CrCl below 30 ml/min. Safety in patients with severe renal impairment may be especially relevant in cases with additional renal impairment secondary to TLS and differentiation syndrome. Please be also referred to the safety section and discussion on "Populations not studied in clinical trials" in the RMP section.

A study in subjects with hepatic impairment has not been conducted with AG-221. A population PK analysis based on the cumulative data suggested markers of liver function, such as albumin, alkaline phosphatase, alanine transaminase and aspartate transaminase are no significant covariates on AG-221 plasma exposure. In the amendment to the population pharmacokinetics and exposure-response analyses report of AG-221 it was mentioned that in the exposure-safety analysis, higher total bilirubin levels were found to be associated with high drug exposure. With the revision of the model after addition of Phase 3 data, it is expected that also the covariate analyses will be redone.

Study CC-90007-CP-003 to assess PK in subjects with moderate and severe hepatic impairment has been initiated in the US. As requested in den D120 ChMP LoQ, the applicant submitted more detailed information on the planned study design of the study on PK in subjects with moderate and severe hepatic impairment (Study Protocol) and the proposed timelines.

Inter-Individual variability was more pronounced and rather high in subjects with advanced hematologic malignancies than in healthy volunteers. No data on intra-individual variability have been provided.

No formal clinical drug interaction studies have been performed; enasidenib metabolism was examined using human liver microsomes, recombinant cytochrome (CYP) and uridine diphosphate glucuronosyltransferase (UGT) enzymes. The absence of clinical drug interactions studies is mentioned in the currently proposed SmPC.

Based on the results of the *in vitro* studies and population pharmacokinetic analysis of patients with advanced haematologic malignancies, the current SmPC states with regard to possible interactions relevant for enasidenib PK ("victim drug")) "*In vitro studies and population pharmacokinetic analysis of patients with advanced haematologic malignancies suggest that there is low risk for clinically relevant drug interactions when acid controlling agents, or inhibitors or inducers of cytochrome P450 (CYP)*

enzymes, UDP glucuronosyltransferase (UGT) enzymes, or transporters are co administered with enasidenib (see section 5.2). No dose adjustment is recommended for enasidenib in patients co administered with other medicinal products.".

In line with the concerns of theoretically clinically relevant CYP inhibition and/or transporter inhibition (enasidenib as "perpetrator drug") the currently proposed SmPC states adequate warnings in section 4.5 for patients being treated with other medicinal products that are substrates of CYP enzymes, UGT1A1 (uridine diphosphate glucuronosyltransferase) or transporters and have narrow therapeutic index:

"[…] *Patients taking medicinal products that have narrow therapeutic ranges, and that are sensitive to CYP1A2 (e.g. theophylline and tizanidine), CYP2C8 (e.g. paclitaxel), CYP2C9 (e.g. phenytoin and warfarin), CYP2C19 (e.g. S-mephenytoin), and/or CYP2D6 (e.g. thioridazine) should be transferred to other medications at least 5 half-lives prior to commencing enasidenib treatment. Other CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP1A2 substrates should be used with caution, and only if medically necessary.*
[…] *Enasidenib may slow the metabolism of drugs that are substrates for UGT1A1, such as irinotecan, ezetimibe, raloxifene and raltegravir. In patients taking UGT1A1 substrates, respective current SmPC recommendations should be followed for co-administration of those medicinal products with strong UGT1A1 inhibitors. If recommendations are lacking, and the therapeutic index of co-administered UGT1A1 substrates is narrow, patients should be switched to alternate therapies at least 5 half-lives prior to starting enasidenib. Other substrates of UGT1A1 should be used with caution if medically necessary, and with monitoring for adverse events.*
[…] *Patients currently taking medicinal products having narrow therapeutic index and sensitive to the above transporters (e.g. digoxin) should either undergo therapeutic drug monitoring (if applicable) or be transferred to other medications at least 5 half-lives prior to initiating enasidenib treatment, if possible*.[…]"

In response to the D120 ChMP LoQ, the SmPC was amended to highlight that co-administration of enasidenib may decrease the concentrations of combined hormonal contraceptives and that additional contraceptive measures (non-hormonal methods) should be used, which is endorsed.

A drug-drug interaction study is needed to enable assessment of the clinical relevance of the *in vitro* findings.

Pharmacodynamics

Enasidenib's mechanism of action, being a first in class drug substance, is proposed to be a differentiation agent: by inhibition of mutant IDH2R140 and R142 enzymatic activities and resulting suppression of the excessive production the oncometabolite D-2-hydroxyglutarate, a variable reduction of mIDH2 variant allele frequency (VAF), normalization of immature:mature hematopoietic cell ratios and differentiation of leukemic cells into functional mature cells are proposed.

The pharmacodynamic activity of enasidenib was investigated non-clinically *in vitro*, *ex vivo* and *in vivo* as well as clinically based on bone marrow and blood samples from study AML patients in the single-arm Phase 1/2 study AG-221-C-001.

The applicant did not utilise an enantioselective bioanalytical method to analyse the levels of the oncometabolite D-2-HG which is produced by the mutant IDH enzymes, but only determined total racemic 2-HG, although published data had previously described that the D/L-2-HG ratio was a more sensitive marker than total 2-HG (e.g., Wiseman et al., 2015, Leukemia, 2421-22). It is currently unknown whether mIDH1/2-AML is mutually exclusive with metabolic diseases such as L-2-Hydroxyglutaric aciduria, a defect of metabolite repair, or other (un-)physiological conditions

leading to increased concentrations of L-2-HG - and with this changing the D/L-ratio and impairing total 2-HG evaluation. Obviously, in most AML cases total 2-HG would be regarded a mirror of D-2-HG produced by a mutant IDH enzyme. Based on the knowledge derived from the sparse phase I/II study data, it is presumed that an enantioselective BA method would have probably not relevantly improved the PD results of enasidenib. In cell-based assays, enasidenib and its metabolite AGI-16903 were 100-fold more potent at the R140Q mutation *vs.* the R172K/S mutations and the % inhibition of 2-HG production by enasidenib and AGI-16903 was 95% and 92% for the R140Q mutation as compared to 62% and 45% for the R172K/S mutations, respectively.

As a response the applicant provided data about kinetic activities of the mutant isoforms and IC_{50} values of enasidenib at either isoforms. Free C_{max} of enasidenib is sufficiently high to inhibit both isoforms. As enasidenib was specifically designed, its higher efficacy (lower IC_{50}) at the physiologically expressed heterodimers than at homodimers is not fully unexpected. The question how baseline 2-HG levels relate to the catalytic activity of the mutant isoforms was not conclusively answered by the applicant, but the statement that "*Cellular context beyond pure enzyme kinetics must contribute to different 2-HG levels and different sensitivities to leukemic dependence on 2-HG*" from the applicant underlines that further investigations are considered indispensable.

In vivo pharmacology studies were conducted in a U87MG IDH2 R140Q xenograft mouse model. These studies were part of evaluating the intracellular activity of enasidenib and not indicated as an appropriate model for the proposed indication. It is recognised that the numbers of models to interrogate inhibitors of IDH are limited. However, this deficiency cannot be compensated by the expectation that the mechanism of differentiation block might be common to all IDH2 mutations that increase 2-HG. In addition, the extrapolation that enasidenib is more potent in models with the R140Q mutant compared to R172 mutant cannot be drawn from this hypothesis. The only conclusion from the preclinical data is that enasidenib exerts anti-tumour activity in cells containing different IDH mutants.

Also in an *ex vivo* study enasidenib reduced intracellular 2-HG and induced cellular differentiation in R140Q primary human AML bone marrow samples in comparison to control. However, this was done on a very limited number of primary cells (for 2-HG reduction and viable cells: 2 with IDH2 R140Q mutation and 2 with wtIDH2, and for differentiation blasts from 1 patient). As it is stated, since the generation of the original dossier, enasidenib has been further evaluated in primary AML patient samples (Yen, 2017). The results of these studies underline a positive effect of enasidenib in patients with IDH2 mutations. However, since the sample size is furthermore limited (three patients with IDH2-R140Qa and three patients with IDH2-R172K, and three patients with IDH2-WT), it seems questionable if these data could be regarded as a generalized positive effect. Furthermore, it cannot be concluded that enasidenib has a superior effect in patients with the R140 mutation compared to the other IDH2 mutations. Therefore, the term selective activity is misleading.

Furthermore, as also the IDH2 mutations seem to perform differently dependent on the tissue context/cancer entity (Marcucci et al., 2010: "*R172 IDH2 mutations were reported to predict a favorable outcome in patients with gliomas, thereby supporting the notion that the prognostic significance of molecular markers may vary according to distinct biologic and/or therapeutic contexts in which they are evaluated*.") it seems questionable if the used preclinical models are appropriate models for the proposed indication. Further effort is needed and additional convincing clinical data are necessary to conclude a real benefit for r/r AML patients treated with enasidenib.

In the Phase 1 part of study AG-221-C-001 suppression of total 2-HG (Report AG-221-C-001-PKPD) was nearly complete for R140 mIDH2 independently of dose (50-650 mg daily) at cycle 2 D1. Based on these PD results for the R140 mutant the daily 100mg dose seems to be at the upper limit of a sigmoidal dose-response curve.

In contrast, for R172 mIDH2, 2-HG suppression was only observed in some patients while in others even an "inverse suppression" = increase of 2-HG production (to >300%) was observed. Median inhibition ranged from 27.6-56.1% so that a correlation between dose and 2-HG suppression could not be established for R172 mIDH2.Treatment with 100 mg enasidenib led to 2-HG reductions by more than 90% of BL in all responding and non-responding R140 patients, which corresponds to approx. 80ng/ml - this level is comparable to levels of <100 ng/ml in healthy volunteers, as reported by Fathi et al., 2012.

In contrast, while R172 patients with CR had 2-HG reductions of ~82% of BL and non-responders of ~38% of BL, both reached levels of ~300ng/ml under treatment.

An even suppression of the catalytic activity of both mIDH2 isoenzymes with 100mg enasidenib as claimed by the applicant is hence not substantiated by clinical PD data for the R172 mutant. The applicant's conclusion for these results *"This may reflect the drug binding affinity and/or catalytic activity between the variants of the mutant IDH2 enzyme"* emphasizes that they currently do not fully understand the different PD effects of enasidenib on both mutants and have not yet deeply elucidated this. Also, the selection of the 100mg dose for further clinical development is considered somewhat arbitrary from a PD point of view.

The analysis of baseline 2-HG levels (report AG221-C-001-TD-2HG-002) revealed that the BL 2-HG levels were statistically significantly higher with R172 mutant than with R140 mutant; especially, in patients with R172 mutant achieving complete response baseline 2-HG levels were more than 2-fold of those in all R140 patients.

Within the R172 mIDH2 r/r AML patient group the baseline 2-HG levels were statistically significantly higher in those who achieved a CR compared to non-responders, whereas for R140 mIDH2 r/r AML patients no such differences were observed.

In the PD report the applicant discusses that the "*higher baseline 2-HG levels in R172 mIDH2 CR patients compared with NR patients is unlikely to have utility as a predictive biomarker for AG-221 activity*". As well they suggest that "*Possible explanations for the differential relationship of 2-HG suppression and response to AG-221 therapy in R140 versus R172 mIDH2 patients could include a differential threshold for release of differentiation block, potentially related to different co-mutation and/or epigenetic profiles in these subgroups. Further investigation is needed to reveal the underlying differences between these subgroups of patients*".

In fact, the last statement is highly supported. Still after D180 responses it is not yet conclusively elucidated from the available non-clinical and clinical Phase 1/2 data how and why the different IDH2 mutations affect D-2-HG levels in r/r AML differently, if the 2-HG level is a relevant biomarker also for r/r AML as compared to *de novo*/untreated AML in general and especially for enasidenib treatment monitoring. Data showed that there were a lot of R172 patients having not shown a drop in total 2-HG level with enasidenib but even an increase. In view of this the target "*pharmacodynamic activity of enasidenib*" can obviously be better visualised and/or monitored in R140 than in R172 patients. As such, the applicant also admitted that *"data suggest that reduction of total 2-HG levels are necessary, but not sufficient, for eliciting clinical response*."

And adding to this, in >80% of patients 2-HG remained suppressed at time of relapse, suggesting mIDH2-independent relapse mechanisms. Comparably, data from 1 patient only for mutant allele burden showed that VAF drops below LLOQ under enasidenib treatment and increased again displaying relapse.

Variant allele frequency as a measure of IDH2 mutant allelic burden was investigated (Report AG221-C-001-TD-IDH2VAF-002). In the combined Phase 1/2 r/r AML patients, IDH2 %VAF at BL was

comparable between the mutational subgroups with means of ~27%. For mR140, VAF at BL was significantly higher in non-responding patients *vs.* CR patients (30.6 vs. 20.5%). For mR172, no definite correlation was observed between response subgroups.

During enasidenib treatment, median VAF was reduced continuously in the mR140-patient group to median <20% of BL. But in the mR172-group median VAF reduction was not lower than median 90% of BL in peripheral blood, independently of clinical response.

Still, complete response to enasidenib was associated with a strong reduction in VAF in both R140 and R172 mutants, and this was statistically significant compared to respective non-CR and non-responding patients. However, especially for the R172 patients, subgroup sample numbers are too small to draw definite conclusions.

Median OS in subgroups defined by quartiles of baseline mIDH2 VAF (both mutants together) was significantly different between highest and lowest quartile (Q4 *vs.* Q1: HR 2.45 [1.30, 4.63]. Insofar, the significantly shorter median OS for patients especially in the 4th VAF quartile may be an indicator that an individual patient on enasidenib treatment needs to be closely monitored for treatment benefit or better be a candidate for treatment change.

Differentiation of bone marrow mononuclear cells was assessed by flow-based assay (FACS; Report AG221-C-001-TD-Immun) from few patients of Phase 1. Results showed the persistence of flow-MRD in responsive enasidenib treated patients indicating a leukemic blasts reduction due to induction of differentiation but not the leukemic blasts elimination (as instead happens in the case of cytotoxic chemotherapy, where leukemic blasts are replaced with normal blast, flow-MRD negative). This means inhibition of mutant IDH2 enzyme results in differentiation of the immature leukemic blasts into functional and mature GM cells that retain the IDH2 mutation.

Though, in contrast to what was reported for the VAF mutational burden in Report AG221-C-001-TD-IDH2VAF-002 above (=reduction of VAF to ~10% of baseline for mR140), in this report it is discussed that *"in all 5 patients, the VAF of mIDH2 was high (>20%) in mature GM cells pre-AG221, suggesting that mIDH2 clones are able to partially differentiate in untreated patients. mIDH2 VAF persisted or increased in the mature GM population at CR or PR in 4/5 patients, as the proportion of mature cells increased in the bone marrow, indicating that in these patients, > 80% of mature GM cells harbor the mIDH2".*

However, in this analysis only 3-5 patient samples from Phase 1 were investigated, which is considered very low even for exploratory analyses. Hence, conclusions are difficult and highly preliminary. Likewise, some sites analysed MRD by local labs and showed that all 8 patients remained flow cytometry-MRD positive at best response (lowest: 0.016% blasts) with a concomitant mIDH2 VAF positivity of 0.2-58%.

Thus, as expected, due to the putative mechanism of action, MRD negativity is uncommon with enasidenib although definitive conclusions are hampered by limited sample size. Despite this insufficient data basis, the applicant did not incorporate to investigate cell differentiation, using fresh bone marrow, for the patients in the ongoing Phase 3 study similarly.

Several recent publications discussed that the (treatment-persistent) mutant allele frequency and the D/L-ratio of 2-HG could serve as the more reliable markers to monitor MRD, to detect early relapses (e.g., Wiseman et al., Leukemia (2015) 29, 2421-22; Petrova et al., Clin. Biochemistry 16 (2018) 34-39), to predict relapse (Ok et al., Haematologia 2019; 104(2):305-311), or relapse free survival or OS (Parkin et al., J Clin Invest. 2017;127(9):3484-3495).

In so far, the fact that 2-HG remained suppressed at relapse and that mutant IDH2 VAF remains at detectable levels during response underlines that this targeted treatment with enasidenib is not sufficient for a durable clinical benefit in the target r/r AML population.

It would have also been interesting to see whether baseline mIDH2 VAF was correlated with pre-treatment status (e.g., after allo SCT, 1st, 2nd, 3rd relapse) and whether observed changes and clinical response during treatment could have been correlated to that. This remains to be investigated in a larger patient population from the Phase III study.

Co-occurring mutations at BL in efficacy-evaluable r/r AML patients were investigated (Report AG221-C-001-TD-CoMut-002) for both IDH2 mutant subgroups R142 and R170. The co-mutational burden was significantly lower in R172 mIDH2 patients *vs.* R140 mIDH2 patients, with 2.4 *vs.* 3.3 co-mutated genes per patient.

Mutations in SRSF2, NPM1, RUNX1, and FLT3 were significantly more frequent in R140, while mutations in DNMT3A, BCOR, and ARID2 were more frequent in R172 mIDH2 patients. DNMT3A was the most frequent co-mutation with R172 mIDH2 with ~58%.

Good prognostic genes, including NPM1, were observed less frequently than in *de novo* AML. Poor prognostic genes like DNMT3A, ASXL1, and RUNX1 were observed more often. The results for absence of NPM1 in R172 r/r AML are in accordance with earlier findings in *de novo* AML that these 2 mutations are [nearly] mutually exclusive. For *de novo* AML it had also been reported that co-mutation of R140 + DNMT3A had the poorest OS (Papaemmanuil et al., NEJM 2016, 374;23; Meggendorfer M. et al., Blood 2017, 130:2682).

In the overall r/r AML population, patients with NRAS mutations had a lower rate of CR. Likewise, FLT3 co-mutations led to lower CR rate in the 100mg daily group. In contrast, a STAG2 co-mutation (cohesion) increased the CR rate.

The more co-mutations were present the lower was the ORR for enasidenib treatment in the r/r AML patients. A potential necessity to treat patients with R172 mIDH2 differently to R140 due to the different and higher number of co-mutations to increase ORR/DOR/OS, i.e. a likelihood for combination targeted treatment, e.g. against NRAS or FLT3, could thus be envisaged. ORR by co-mutational burden, separately analysed for R140 vs. R172 mutations, confirmed the results from the overall study population.

Published data (see Medeiros BC et al, Leukemia 2017) suggest that IDH2 R172 and R140 mutations might have different effects on prognosis, with patients harbouring an IDH2 R172 mutation having a significantly worse outcome compared to subjects with mIDH2 R140. Based on such evidence, AML with mIDH2-R172 has been even proposed as a completely distinct subclass of AML. It is recognized, however, that cytogenetic and mutational context may influence AML prognosis, possibly explaining contrasting reports on the impact of mIDH2-R172 on survival (see e.g. Papaemmanuil E et al, NEJM 2016), and that further data are required to assess the actual impact of IDH2 mutational site on survival and response to enasidenib. In this regard, additional data from the ongoing Phase III study are awaited and efficacy data stratified by IDH2 mutational site from Phase III study are needed.

According to efficacy results, patient subgroups at different relapse status responded differently, more or less "the earlier the line the better". Although this might be astonishing from a sole mechanistically point of view for a specific enzyme inhibitor in an correspondingly selected population this is clinically not surprizing, considering that in later treatment lines clones of un-eliminated and now untargeted co-mutations prevailed so that the IDH2 mutated clone is no longer the mutation mainly responsible for clinical response and relapse. However, as for the IDH2 mutational burden by pre-treatment line, further subgroup analyses for co-mutational burden based on the currently available small dataset

from this Phase 1/2 study AG-221-C-001 would not result in valuable information and should thus be re-iterated once more comprehensive data from larger confirmatory studies are available.

In view of published data of acquired secondary-resistance IDH2 mutations in R140Q patients (Intlekofer et al., Nature, 2018) the applicant was asked to review their data whether patients were recorded for whom similar mutations at the binding pocket were detected already at baseline prior to initiation of enasidenib treatment, as a prognosis of enasidenib treatment-resistance could be envisaged. The applicant stated that no own clinical study data of potentially resistant IDH2 mutations at the binding pocket, which were detected prior to enasidenib initiation, are available to date. Neither, the applicant had investigated %MAF/VAF for the mutants, which is deemed relevant in terms of relapse prediction, as relapse from response to enasidenib treatment is not necessarily due to mIDH2-related resistance but relevantly due to growth of un-targeted clones. Of cause this also depends on the nature and VAF of the other co-mutations. The applicant admitted that this is necessary and important work to be done and committed to submit such data as soon as available. This is included as a PAM in case of approval (see section 8.1).

Concluding, several of the yet discussed points about primary pharmacology are still unclear after D180+x to understand the pharmacodynamic basis of enasidenib's activity on mutant R140- and mutant R172-IDH2 enzymes. These relate, at least, to:

- which are "thresholds of IDH2 positivity" in the proposed r/r AML population, i.e. to establish a mutIDH2 status, e.g., based on 2-HG level, %VAF and/or other biomarkers for R142 and R170 mIDH2 separately, necessary and sufficient and, above all, clinically relevant to initiate or not initiate treatment with enasidenib?
- is there a possibility for treatment monitoring, e.g. by 2-HG and %VAF?
- despite mIDH2-innate PD markers, how far do number and profile of co-existing mutations play a role for the extent of pharmacodynamic and clinical response to enasidenib and overall survival in the different mutant isoforms?

At least on basis of the currently available phase I/II single-arm study data it is concluded that only two-dimensional (univariate) and time-point-related PD correlation approaches to predict enasidenib treatment effects (in contrast to multivariate and longitudinal), such as BL-2-HG *vs.* OR or %VAF *vs*. OS, are insufficient and incomplete in a usually multiclonal disease like mIDH2-r/r AML with 2 non-similar mutation isoforms.

In addition, due to the newly started discussions about clinically relevant treatment effects of enasidenib on transfusion dependence and the current data also not establishing a definite correlation of response with transfusion independence, the applicant is now requested to provide new translational PD analyses for this secondary endpoint, both for the total patient group of r/r AML patients and especially for the separated R140/R172 mutant isoforms; see LOoI.

Overall, from a pharmacodynamic point of view several questions need further investigation, both from the available data set and on basis of a larger patient population as from the confirmatory controlled Phase III study, before conclusions on clinical benefit can be drawn.

Secondary pharmacodynamics

With regard to cardiac safety, the exposure-response analysis from ECG results obtained from the main study AG221-C-001, confirmed the results from PK studies in HV, that the potential for significant concerns regarding QTc prolongation with enasidenib is minimal. The information related to QTc proposed for section 5.1 is considered appropriate.

The applicant adequately clarified why PD interactions of enasidenib or its metabolite AGI-16903 via adenosine receptor antagonism are unlikely for A1 and A2a receptors. For A3 receptors, in contrast, a functional antagonism of enasidenib cannot be ruled out from the available IC_{50} values. To date, clinical aspects of such a potential A3 antagonism have not been observed; however, interactions with future A3 targeting drugs cannot be completely ruled out.

Exposure-response relationship

The exposure-efficacy analyses showed that there is no apparent relationship between systemic enasidenib exposure levels and the clinical best responses, in the range of exposures evaluated at clinical daily doses from 50 mg to 650 mg, using investigator-assessed best response, respectively. In view of the fact that exposures were comparable for R140 and R172 mutated IDH2 patients, it is considered not relevant to analyse exposure-response separately for these subgroups.

In absence of any consistently observed dose-(or exposure-) response relationship for either the investigated pharmacodynamic markers, and for both the R140 and R172 IDH2-mutants the applicant decided to further investigate the 100mg dose in phase 2 for the full population.

3.3.4. Conclusions on clinical pharmacology

Pharmacokinetic properties of enasidenib have been overall adequately described, however, there are aspects that have to be further discussed by the applicant (see LoQ).

The pharmacodynamic proof of concept dataset based on data from the Phase 1/2 study AG221-C-001 presented to date is considered too small and results hence preliminary and exploratory only. Even for a new medicinal product in a r/r AML patient population with limited treatment options it is considered inadequate to show some clinical activity without understanding the reasons for this.

As a result, the applicant is requested to perform the discussed PD analyses similarly in the ongoing confirmatory Phase 3 study in r/r AML (and further upcoming larger studies) for corroboration of the presented PD data and investigation of missing information. As also concluded by the applicant themselves: "*Larger prospective analyses are needed to validate these findings.*"

In addition, still other concerns need to be resolved.

3.3.5. Clinical efficacy

Introduction

To support this MAA for enasidenib (Idhifa) as monotherapy for the treatment of adult patients with r/r AML and IDH2 mutation, the Applicant submitted the results from one single pivotal trial (phase 1/2 study AG221-C-001).

Considering that the AG221-C-001 study is a single arm study without a comparator arm, the Applicant also provided the following retrospective data to try to put the clinical effectiveness of enasidenib into context:

- a systematic review of published literature and
- a comparison of the AG221-C-001 data versus AML registry data collected in R/R AML patients with an IDH2 mutation treated with conventional treatments in a real-world setting (the mentioned registries being the AMLSG (Germany) and PETHEMA (Spain)).
- A propensity score matching analysis of study AG221-C-001 vs French Chart Review and vs AMLSG

Furthermore, a randomised controlled phase 3 study (AG-221-AML-004) is ongoing.

For more details please refer to section 2.3. and 5.1.3 of this AR.

Dose-response studies

A dose titration was performed in the phase 1 part (escalation) of the main study (AG221-C-001). However, as described in the PD section a correlation between plasma enasidenib AUC_{0-24} levels and the clinical best responses was not apparent based on the data of different doses from all patients in phase 1 of the study.

Main clinical study

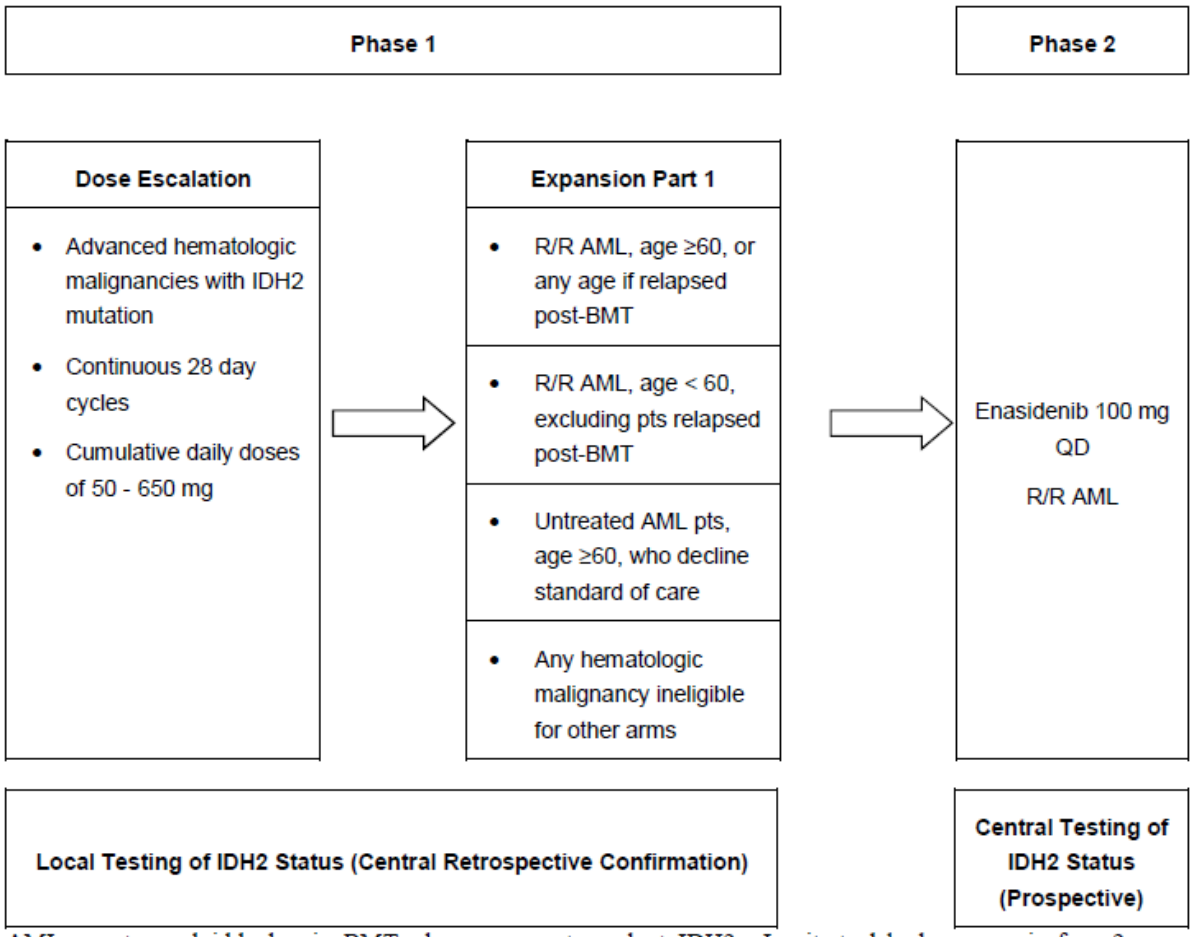
AG221-C-001

Title: "*A Phase 1/2, Multicentre, Open-Label, Dose Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 In Subjects With Advanced Hematologic Malignancies With an IDH2 Mutation*"

(EudraCT number: 2013-001784-23) (ClinicalTrials.gov Id: NCT01915498)

The efficacy claims are supported by a single pivotal study, namely the first-in-human study AG221-C-001, an uncontrolled, open-label, multi-centre phase 1/2 study in subjects who have advanced haematologic malignancies with an IDH2 mutation, including R/R AML. The efficacy data presented for Study AG221-C-001 are focussing only on the data from the 214 R/R AML subjects treated with enasidenib monotherapy 100 mg daily based on a data cut-off date of 01 Sep 2017.

Figure eff 01. Study diagram (AG221-C-001)



AML = acute myeloid leukemia; BMT = bone marrow transplant; IDH2 = Isocitrate dehydrogenase, isoform 2; pts = patients; QD = once daily; R/R = relapsed/refractory.

Methods

- **Study participants**

Key inclusion criteria:

- Diagnosis of refractory or relapsed AML (R/R AML) according to WHO criteria

  Phase 1 (dose escalation + dose expansion)

  - No further specifications regarding R/R AML defined in this study phase

  Phase 2

  - Subjects who relapse after allogeneic HSCT
  - Subjects in second or later relapse
  - Subjects who are refractory to initial induction or re-induction treatment
  - Subjects who relapse within 1 year of initial treatment, excluding patients with favourable-risk status according to NCCN 2015 [i.e.: inv(16), +(16;16), t(8;21), t(15;17)]

- Documented IDH2 gene-mutated disease [in phase 1 dose escalation and dose expansion based on local evaluation (retrospective centralised retesting performed), and in phase 2 based on central testing]
- Subjects were ≥18 years of age
- Subjects had an ECOG PS of 0 to 2
- Platelet count ≥20,000/μL (transfusions to achieve this level were allowed). Subjects with a baseline platelet count of <20,000/μL due to underlying malignancy were eligible with medical monitor approval.
- Subjects had adequate hepatic function as evidenced by:
    - Serum total bilirubin ≤1.5 × ULN, unless considered due to Gilbert's disease, a gene mutation in UGT1A1, or leukemic organ involvement, following approval by the medical monitor.
    - AST, ALT, and ALP ≤3.0×ULN, unless considered due to leukemic organ involvement
- Subjects had adequate renal function as evidenced by:
    - Serum creatinine ≤2.0×ULN or
    - Creatinine clearance >40 mL/min based on the Cockroft-Gault GFR estimation

Key exclusion criteria:

- Subjects for whom potentially curative anticancer therapy was available.
- Subjects with NYHA Class III/IV congestive heart failure or LVEF <40% by echocardiogram or MUGA scan obtained within approximately 28 days of C1D1.
- Subjects with uncontrolled hypertension.
- Subjects with known unstable or uncontrolled angina pectoris.
- Subjects with a known history of severe/ uncontrolled ventricular arrhythmias.
- Subjects with a QTcF interval ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (eg heart failure, hypokalemia, family history of long QT interval syndrome) at screening.
- Subjects taking medications that are known to prolong the QT interval unless.

- **Treatments**

214 R/R AML patients were treated with enasidenib 100 mg monotherapy daily (starting dose), of which 109 were from phase 1 and 105 were from phase 2.

Phase 1 (dose expansion)
In the dose expansion part of phase 1 a dose of enasidenib 100 mg QD was selected for initial evaluation. The protocol allowed for exploration of different dosing regimens as warranted based on the emerging clinical safety, PK, PD and clinical activity data.

Phase 2:

Enasidenib was to be taken orally QD in an uninterrupted daily schedule with no rest period between 28-day treatment cycles. The daily dose was to be taken at approximately the same time each day, with a glass of water. Subjects were to swallow tablets whole and not chew the tablets. Each daily dose was to be taken at least 2 hours after fasting (water was allowed) and food intake was to be delayed for at least 1 hour after study drug administration.

Intra-subject dose escalation to 200 mg QD was permitted after treatment with enasidenib 100 mg QD during the initial treatment cycle if the following occurred:

- absolute neutrophil count (ANC) < 0.5 x 109/L after being on enasidenib for the first cycle without ≥ Grade 3 AEs suspected by the investigator to be related to enasidenib; or
- no partial response achieved after being on enasidenib for at least 2 cycles without ≥ Grade 3 AEs suspected by the investigator to be related to enasidenib; or
- evidence of morphologic relapse or progressive disease.

If benefit was demonstrated at an increased dose level, then that dose level was to be maintained during the subsequent treatment cycles.

In case of toxicities enasidenib dose was to be reduced in multiples of 50 mg. Any subject who was unable to tolerate 50 mg QD of enasidenib was to be discontinued from study treatment. Re-escalation back to the starting dose and/or an intermediate dose was permitted.

Subjects were to continue treatment with enasidenib until disease progression or development of unacceptable toxicity.

- **Objectives (as to study protocol)**

Phase 1 (dose escalation and dose expansion)

Primary objectives:

- Assessment of safety and tolerability of treatment with enasidenib administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle in subjects with advanced hematologic malignancies
- Determination of the MTD or maximum administered dose (MAD) and/or the RP2D of enasidenib in subjects with advanced haematologic malignancies

Secondary objectives:

- Description of the dose-limiting toxicities (DLTs) of enasidenib in subjects with advanced haematologic malignancies
- Characterisation of the PK of enasidenib and its metabolite in subjects with advanced haematologic malignancies
- Characterisation of the PK/PD relationship of enasidenib and 2-HG
- Characterisation of the clinical activity associated with enasidenib in subjects with advanced haematologic malignancies

Phase 2

Primary objectives:

- assessment of the efficacy of enasidenib as treatment for subjects with R/R AML with an IDH2 mutation

Secondary objectives:

- evaluation of the safety profile in subjects with R/R AML with an IDH2 mutation
- characterisation of the PK of enasidenib and its metabolite in subjects with R/R AML with an IDH2 mutation
- characterisation of the PK/PD relationship of enasidenib and 2-HG

- **Endpoints (as to study report)**

Efficacy endpoints (phase 1):

- Investigator-assessed overall response rate (ORR), CR rate (CRR), CR + CRi/CRp rate, and duration of response
- Qualitative improvement of response over time including time to response, time to best response, and duration of response, and improvement in haematology over time
- Additional assessments of clinical benefit, including 56-day transfusion independence, overall survival, event-free survival (EFS), rates of infection, bleeding, and neutropenia during response periods

Efficacy endpoints (phase 2):

- Investigator assessed and IRAC assessed overall response rate (ORR), CR rate (CRR), CR + CRi/CRp rate, and duration of response
- Qualitative improvement of response over time including time to response, time to best response, and duration of response, and improvement in haematology over time
- Additional assessments of clinical benefit, including 56-day transfusion independence, overall survival (OS), event-free survival (EFS), rates of infection, bleeding, and neutropenia during response periods

Relevant endpoint definitions used (as to modified International Working Group Response Criteria)

- Complete remission (CR): Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 109/L (1000/µL); platelet count >100 x 109/L (100,000/µL); independence of red cell transfusions
- CR with incomplete platelet recovery (CRp): All CR criteria except for residual thrombocytopenia (platelet counts <100 x 109/L [100,000/µL])
- CR with incomplete haematologic recovery (CRi): All CR criteria except for residual neutropenia (absolute neutrophil count <1.0 x 109/L [1000/µL])
- Morphologic leukaemia free state (MLFS): Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
- Partial remission (PR): Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent

- Resistant disease: Failure to achieve CR or CRi (general practice; Phase 2/3 trials), or failure to achieve CR, CRi or PR (Phase 1 trials); only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
- Relapse: Bone marrow blasts ≥5 percent; or reappearance of blasts in the blood; or development of extramedullary disease

- **Sample size**

Phase 1:

Assuming that identification of the MTD/MAD required the evaluation of 13 dose levels/schedules of enasidenib with up to 5 subjects per dose level, with the exception that the MTD requires 6 subjects, then 66 subjects were to be enrolled during the dose escalation part of the study. Additional subjects may have been needed for cohort expansion during dose escalation, for the replacement of subjects who are not evaluable for PK/PD, safety, or clinical activity, or for evaluation of alternative dosing regimens other than the planned escalation scheme or the MTD, to optimize the RP2D and regimen(s).

Four cohorts of approximately a minimum of 25 additional subjects in specific haematologic malignancy subsets (total a minimum of 100 subjects) were to be enrolled in Part 1 expansion of the study.

Based on this, it was estimated that a minimum of 166 subjects were to be enrolled in the Phase 1 part.

Phase 2:

The Phase 2 portion of the trial was to enrol approximately 125 subjects with R/R AML with an IDH2 mutation.

The underlying calculation for the inclusion of 125 subjects according to the study protocols (amendment 3 and 4) was the following:

"Based on a sample size of n=125 subjects, an observed CR rate of at least 22% (at least 28 responses in 125 subjects) result in an exact binomial 95% CI with a lower bound greater than 15%. If 28 complete remissions in 125 subjects are observed (22.4% observed CR rate) the 95% CI will be (15.4%, 30.7%). This will be considered as evidence of clinically significant activity of AG-221.

An observed objective response rate (ORR) of at least 33% in 125 subjects (at least 42 responses in 125 subjects) will result in an exact binomial 95% CI with a lower bound greater than 25%, which is clinically meaningful in this setting and exceeds the ORR expected with available therapies (Roboz, et al. 2014). If 42 responses in 125 subjects are observed (33.6% observed ORR), the 95% CI will be (25.4%, 42.6%). This will also be considered as evidence of clinically significant activity of AG-221."

- **Randomisation**

Not applicable for an uncontrolled trial.

- **Blinding (masking)**

Not applicable for an uncontrolled trial.

- **Statistical methods**

The study data was analysed and reported based on all subjects' data from the Phase 1 dose escalation, Part 1 Expansion, the combined Phase 1, Phase 2, and the combined Phase 1/2 up to the data cut-off

date of 01 Sep 2017 when the follow-up is deemed adequate for the assessment of the primary and key secondary efficacy endpoints. The Full Analysis Set (FAS) including all subjects who received at least 1 dose of study treatment was the primary analysis population for efficacy and was the default analysis set for all analyses, unless otherwise specified.

The ORR, the CRR, and the rate of rate of CR +CRi/CRp in were summarized by the percentage of responses with 2-sided exact binomial 95% confidence interval (CI).

Kaplan-Meier (KM) method was utilized to estimate duration of responses (DoR), duration of complete response (DoCR), OS, and EFS. The 25th percentile, median and 75th percentile time with two-sided 95% CI was provided. In addition, KM methods were used to estimate the survival probabilities at 3, 6, 9, and 12 months.

Among subjects who had a response of CR, CRi, CRp, PR, or mCR/MLFS by investigator assessment, DoR was calculated as the date of the first documented response to the date of the first documented disease relapse, progression or death due to any cause, whichever occurred first.

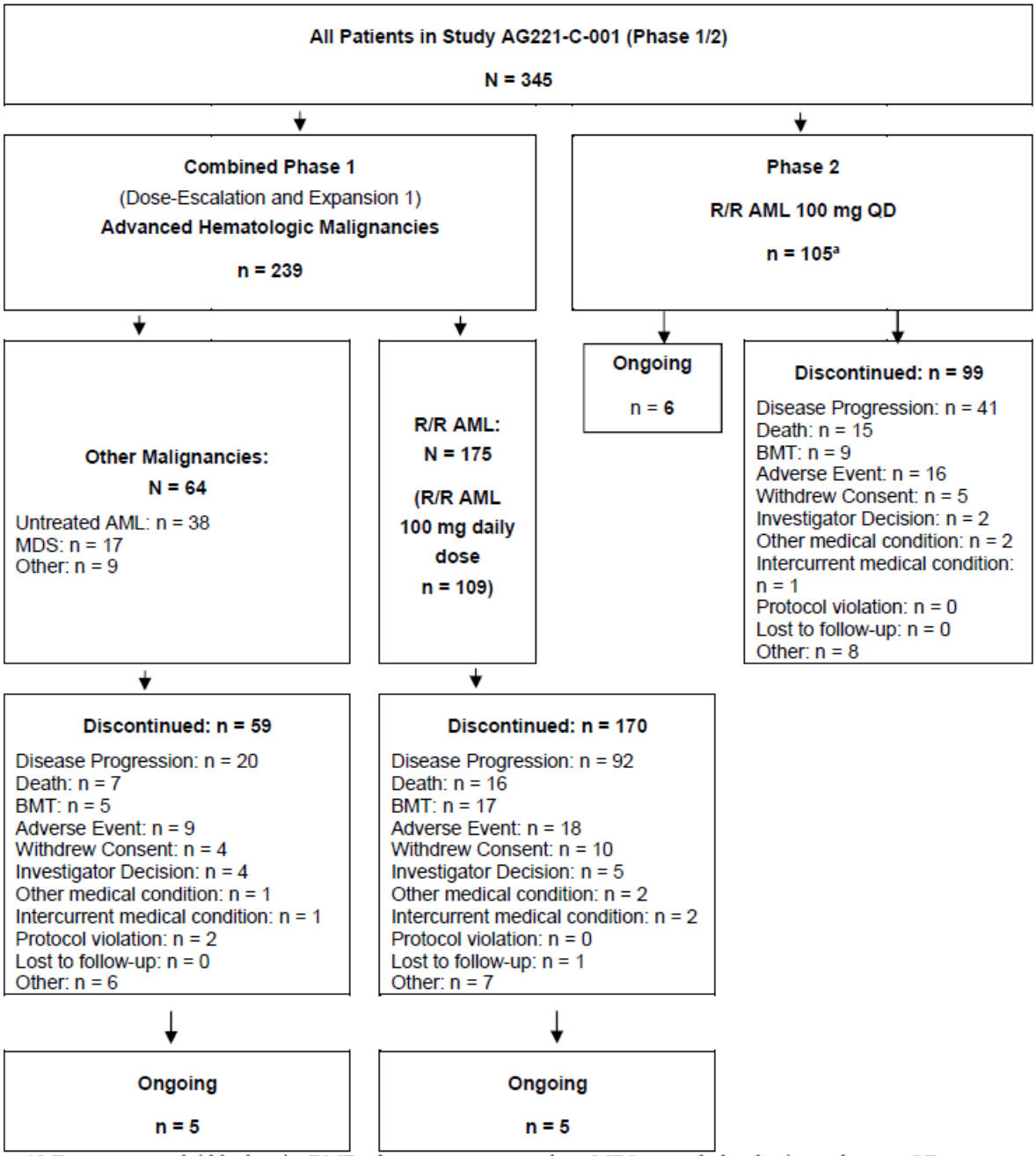
Overall survival was defined as the time from first dose to the date of death due to any cause. Subjects alive were censored at the last date known to be alive or a pre-specified data cut-off date, whichever was earlier.

Event-free survival was defined as the interval from the date of the first dose to the date of documented relapse, progression or death due to any cause, whichever occurred first.

Results

- **Participant flow**

Figure eff 02. Disposition in study AG221-C-001 (Full analysis set)



AML = acute myeloid leukemia; BMT = bone marrow transplant; MDS = myelodysplastic syndromes; QD = once daily; R/R = relapse/refractory.

[a] One subject in Phase 2 with newly diagnosed AML is not represented in this figure.

Source: 'Summary of clinical efficacy' page 36

The main reason for discontinuation of treatment across both phases of the study was disease progression. This accounted for ~47% (101/214) of the R/R AML subjects in the combined Phase 1/2 population who received a daily dose of 100 mg enasidenib (12% due to AE or DLT; 11% due to death; 10% due to HSCT) (Source: table 14.1.3.7).

The reason for study discontinuation in the majority of subjects across both phases of the study was death, which accounted for ~66% (141/214) of the R/R AML subjects in the combined Phase 1/2 population who received a daily dose of 100 mg enasidenib (7% due to withdrawal of consent; 9% due to 'other' reasons) (Source: table 14.1.3.7).

- **Numbers analysed**

Table eff 04. Analysis populations phase 1 and phase 2

	R/R AML (N = 178) [a] n (%)	R/R AML 100 mg QD (N = 107) [b] n (%)
	Phase 1 comb.	Phase 2
Full Analysis Set (FAS)[c]	175 (98.3)	105 (98.1)
Safety Analysis Set (SAS)[d]	175 (98.3)	105 (98.1)
Evaluable Analysis Set (EAS)[e]	143 (80.3)	84 (78.5)

a Three subjects passed screening, but were not treated. These 3 subjects were not included in the analysis sets.
b Two subjects passed screening, but were not treated. These 2 subjects were not included in the analysis sets.
c Includes all subjects who were enrolled and received at least one dose of treatment. Subjects will be classified according to the assigned dose level and schedule.
d Includes all subjects who were enrolled and received at least one dose of treatment. Subjects were classified according to the treatment received.
e Includes all subjects in the full analysis set for whom the baseline response assessment and at least one post-baseline response assessment at Day 28 or later are available and evaluable. Subjects were excluded if they did not have an advanced hematologic malignancy, did not have documented IDH2 gene-mutated disease, or received concomitant treatment for their malignancy other than enasidenib.
Source: CSRs study AG221-C-001 phase 1 (table 9) and phase 2 (table 5)

Annotation: Of the 175 subjects in the FAS from Phase 1, 109 were treated with the 100 mg daily dose and were included in the efficacy analyses.

- **Recruitment**

First patient treated (phase 1):	20 Sep 2013
First patient treated (phase 2):	25 Jun 2015
Last patient last visit:	01 Sep 2017 data cut off
Release date of CSR:	21 Feb 2018
Study status:	ongoing (recruitment: complete; treatment ongoing: n=16; study ongoing: n=54)

- **Conduct of the study**

Changes in the conduct of the study or planned analysis

Protocol amendments

The original protocol of study AG221-C-001 (dated 03 Jun 2013) was amended 7 times:

- Amendment 1 (dated 18 Jul 2013) (before study start)
- Amendment 2 (dated 23 Sep 2013) (3 days after study start)
- Amendment 3 (dated 16 Apr 2014)
- Amendment 4 (dated 02 Feb 2015)
- Amendment 5 (dated 18 May 2015)
- Amendment 6 (dated 14 Oct 2015) (after first patients treated in phase 2)
- Amendment 7 (dated 07 Oct 2017) (after the data cut-off date)

Protocol compliance

Phase 1

Overall, a total of 42/175 subjects with R/R AML (24.0%) in combined Phase 1 (dose escalation + dose expansion) had at least 1 protocol violation.

The most frequently observed violation was concomitant medication and/or procedure (13.7%, 24/175). These were primarily subjects receiving prohibited medications, the majority of which were corticosteroids (for treatment of or prophylaxis for transfusion reaction, differentiation syndrome, respiratory condition infection, nerve disorder, or arthritic condition), antiinfectives or hydroxyurea (for treatment of leukocytosis without medical monitor approval).

The GCP issues (6.9%, 12/175) were mainly (n=10) the failure to report an SAE within the 24-hour reporting period. Although these events were not reported within that time frame, they were ultimately reported and captured in the database.

The frequency and type of protocol violations were generally similar in the subset of subjects with R/R AML who received the 100 mg daily dose compared with the overall R/R AML population.

Phase 2

Overall, a total of 17/106 subjects (16.0%) in the overall Phase 2 population had at least 1 protocol violation.

The most frequently observed violations were entry criteria and GCP issues (5.7%, 6 subjects each).

Four of the 6 subjects that did not meet the 'R/R AML inclusion criterion' (#2) were diagnosed with R/R AML at screening; however, the screening bone marrow aspirate contained <5% blasts. As to the Applicant additional supportive data available at or near the time of screening were identified that further substantiated the diagnosis of R/R AML. One of the 6 subjects had newly diagnosed AML and is included in this protocol violation section but not in the efficacy and safety analyses presented.

The GCP issues were the failure to report an SAE within the 24-hour reporting period. Although these events were not reported within that time frame, they were ultimately reported and captured in the database.

GCP inspection

FDA performed the following GCP inspections for study AG221-C-001:

- Sponsor inspection:
    - Celgene Corp, Summit, NJ, USA) (13, 15-17 March 2017)
- Site inspections for the following sites:
    - Stanford Cancer Center, Stanford, CA, USA (11-29 April 2016)
    - Memorial Sloan-Kettering Cancer Center, New York, NY, USA (13-16 March 2017)
    - Institut Gustave Roussy – Service DITEP, Villejuif, France (24-27 April 2017)
    - University of Texas MD Anderson Cancer Center, Houston, TX, USA (2-5 May 2017

EMA performed the following routine GCP inspections for study AG221-C-001 (GCP/2018/023):

- CRO
- Site inspection:
    - Institut Gustave Roussy – Service DITEP, Villejuif, France (05-09 Nov 2018)

For further information of the performed FDA und EMA inspections of trial AG221-C-001 please refer to section 1 "GCP inspections" above.

- **Baseline data**

Table eff 05. Key Demographics (FAS for R/R AML + enasidenib 100 mg QD)

	Combined Phase 1/2 100 mg (N = 214) n (%)	Phase 1 100 mg (N = 109) n (%)	Phase 2 100 mg (N = 105) n (%)
Age (years)			
Median (Min, Max)	68.0 (19.0, 100.0)	67.0 (19.0, 100.0)	68.0 (32.0, 89.0)
Age Categories (years) (n, %)			
< 60	63 (29.4)	38 (34.9)	25 (23.8)
≥ 60 - < 70	56 (26.2)	22 (20.2)	34 (32.4)
≥ 70 - < 75	44 (20.6)	23 (21.1)	21 (20.0)
≥ 75	51 (23.8)	26 (23.9)	25 (23.8)
Sex (n, %)			
Male	109 (50.9)	46 (42.2)	63 (60.0)
Female	105 (49.1)	63 (57.8)	42 (40.0)

Source: Summary of clinical efficacy' page 95, table 19

Table eff 06. AML History and Baseline Laboratory Values (FAS for R/R AML + enasidenib 100 mg QD)

	Combined Phase 1/2 100 mg (N = 214)	Phase 1 100 mg	Phase 2 100 mg (N = 105)
WHO Classification of AML (n, %)			
AML with Recurrent Genetic Abnormalities	28 (13.1)	7 (6.4)	21 (20.0)
AML with Myelodysplasia-Related Changes	46 (21.5)	27 (24.8)	19 (18.1)
Therapy-related Myeloid Neoplasms	5 (2.3)	1 (0.9)	4 (3.8)
AML not Otherwise Specified	115 (53.7)	62 (56.9)	53 (50.5)
Missing	20 (9.3)	12 (11.0)	8 (7.6)
Prior MDS (n, %)			
Yes	46 (21.5)	17 (15.6)	29 (27.6)
No	168 (78.5)	92 (84.4)	76 (72.4)
Time from Initial Diagnosis (months)[a]			

n	179	98	81
Median (Min, Max)	10.4 (1.2, 129.1)	9.6 (1.2, 129.1)	11.7 (1.3, 86.3)
Refractory/Relapsed Status (n, %)			
Primary refractory	84 (39.3)	48 (44.0)	36 (34.3)
Relapsed	130 (60.7)	61 (56.0)	69 (65.7)
R/R AML Subpopulation (n, %)[b]			
Total Subjects	196 (91.6)	96 (88.1)	100 (95.2)
Relapse after allogeneic transplantation	29 (14.8)	12 (12.5)	17 (17.0)
Second or later relapse	27 (13.8)	14 (14.6)	13 (13.0)
Refractory to initial induction or re-induction treatment	64 (32.7)	36 (37.5)	28 (28.0)
Relapse within 1 year of initial treatment [c]	55 (28.1)	26 (27.1)	29 (29.0)
Failed 2 or more cycles of first line therapy [d]	57 (29.1)	25 (26.0)	32 (32.0)
Cytogenetic Risk Status (n, %)[e]			
Intermediate-Risk	108 (50.5)	51 (46.8)	57 (54.3)
Poor-Risk	55 (25.7)	29 (26.6)	26 (24.8)
Failure	7 (3.3)	2 (1.8)	5 (4.8)
Missing	44 (20.6)	27 (24.8)	17 (16.2)
Bone Marrow Blasts, Local (%)[f]			
n	210	108	102
Median (Min, Max)	46.5 (0.0, 98.0)	51.5 (0.0, 96.0)	45.5 (2.0, 98.0)
Bone Marrow Blasts, Category (%)			
< 20%	47 (22.0)	25 (22.9)	22 (21.0)
20% to < 30%	21 (9.8)	7 (6.4)	14 (13.3)
30% to < 50%	40 (18.7)	22 (20.2)	18 (17.1)
≥ 50%	102 (47.7)	54 (49.5)	48 (45.7)
Missing	4 (1.9)	1 (0.9)	3 (2.9)
Gene Mutation (IDH2) Analysis (n, %) [g]			
R140	162 (75.7)	83 (76.1)	79 (75.2)
R172	51 (23.8)	25 (22.9)	26 (24.8)
Missing	1 (0.5)	1 (0.9)	0
Haemoglobin (g/L)			
n	213	109	104
Median (Min, Max)	90.0 (69.0, 156.0)	93.0 (69.0, 138.0)	89.0 (70.0, 156.0)
Platelets (x 10^9/L)			
n	213	109	104
Median (Min, Max)	37.0 (1.0, 1288.0)	39.0 (1.0, 372.0)	36.0 (2.0, 1288.0)
ANC (x 10^9/L)			
n	212	108	104

Median (Min, Max)	0.4 (0.0, 70.0)	0.4 (0.0, 5.6)	0.4 (0.0, 70.0)
WBC (x 10^9/L)			
n	213	109	104
Median (Min, Max)	2.3 (0.2, 93.8)	3.0 (0.2, 88.2)	2.0 (0.2, 93.8)
Creatinine Clearance (mL/min)			
n	213	109	104
Median (Min, Max)	83.4 (29.1, 237.4)	85.4 (29.1, 237.4)	80.6 (30.4, 225.1)
ECOG PS (n, %)			
0	49 (22.9)	25 (22.9)	24 (22.9)
1	132 (61.7)	68 (62.4)	64 (61.0)
2	32 (15.0)	16 (14.7)	16 (15.2)

a Calculated from date of AML initial diagnosis to start date of regimen.
b Total number of R/R AML subjects who met any of the criteria below; a subject could have met more than one criterion. For each subpopulation, percentages are based on the total number of R/R AML subjects who met any of the criteria.
c Excluding subjects with favourable-risk status according to NCCN Guidelines (NCCN v1.2015).
d Consisting of an intermediate intensity chemotherapy, hypomethylating agent or low dose cytarabine (failed is defined as refractory or relapsed after receiving regimens involving low-intensity therapy).
e Cytogenetic samples were not required as part of the study per early versions of the protocol. Cytogenetic sampling was added via Amendment 4. A retrospective collection for cytogenetic data was performed for all subjects, however in some cases cytogenetics were not performed or the data were not available.
f Four subjects in the combined Phase 1 were diagnosed with R/R AML at Screening, however the Screening bone marrow aspirate contained < 5% blasts.
g Based on results from local laboratories for Phase 1 and from central laboratories for Phase 2. In Phase 2 the first 15 subjects underwent central laboratory testing at using a next-generation sequencing assay and the remaining subjects were tested using the.
Source: 'Summary of clinical efficacy', table 20, page 97-99

Table eff 08. Prior anticancer therapies (FAS for R/R AML + enasidenib 100 mg QD)

	Combined Phase 1/2 100 mg (N = 214)	Phase 1 100 mg (N = 109)	Phase 2 100 mg (N = 105)
Prior Systemic Anticancer Therapies			
n (%)	214 (100.0)	109 (100.0)	105 (100.0)
Number of Prior Anticancer Regimens (n, %)			
Median (Min, Max)	2.0 (1.0, 5.0)	1.0 (1.0, 5.0)	2.0 (1.0, 5.0)
1	101 (47.2)	59 (54.1)	42 (40.0)
2	65 (30.4)	27 (24.8)	38 (36.2)
3	30 (14.0)	17 (15.6)	13 (12.4)
4	12 (5.6)	3 (2.8)	9 (8.6)
≥ 5	6 (2.8)	3 (2.8)	3 (2.9)
Prior Stem Cell Transplants for AML (n, %)			
Yes	29 (13.6)	12 (11.0)	17 (16.2)
No	185 (86.4)	97 (89.0)	88 (83.8)
Time (months) from Last Prior HSCT to First Dose of Enasidenib			
n	26	12	14
Median (Min, Max)	16.9 (4.8, 53.5)	14.1 (4.8, 44.1)	17.0 (6.4, 53.6)

Source: 'Summary of clinical efficacy', table 22, page 102

The most common systemic therapies for AML received by subjects prior to entering this study were antimetabolites (98.6%), specifically, cytarabine (73.8%), azacitidine (29.0%) and decitabine (27.1%), and cytotoxic antibiotics and related substances (68.7%), specifically, idarubicin (36.4%) and daunorubicin (31.3%). The proportion of subjects who received these therapies was comparable across the 2 phases of the study except for azacitidine [phase 2: 37/105 (35.2%); phase 1: 25/109 (22.9%)].

- **Outcomes and estimation**

Response assessment

Table eff 09. Investigator assessed best responses (FAS for R/R AML + enasidenib 100 mg QD)

	Combined Phase 1/2 100 mg (N = 214)	**Phase 1 100 mg (N = 109)**	**Phase 2 100 mg (N = 105)**
CR Rate (n [%]) (95% CI)[a]	42 (19.6) (14.5, 25.6)	21 (19.3) (12.3, 27.9)	21 (20.0) (12.8, 28.9)
KM Median **Duration of CR** (months)[b] (95% CI)	7.4 (6.5, 16.3)	16.3 (5.6, NA)	6.7 (3.7, 7.4)
CR+CRi/CRp Rate (n [%]) (95% CI)[a]	62 (29.0) (23.0, 35.5)	29 (26.6) (18.6, 35.9)	33 (31.4) (22.7, 41.2)
KM Median **Duration of CR+CRi/CRp** (months)[b] (95% CI)	6.7 (5.3, 9.7)	8.8 (5.1, 24.0)	6.5 (3.7, 7.4)
ORR (CR+CRi+CRp+PR+MLFS)[c] (n [%]) (95% CI)[a]	83 (38.8) (32.2, 45.7)	44 (40.4) (31.1, 50.2)	39 (37.1) (27.9, 47.1)
KM Median **Duration of ORR** (months)[b] (95% CI)	5.6 (3.8, 7.4)	5.6 (3.3, 9.7)	5.6 (3.7, 7.4)
Non- CR Responses			
CRi/CRp	20 (9.3)	8 (7.3)	12 (11.4)
PR	9 (4.2)	5 (4.6)	4 (3.8)
MLFS	12 (5.6)	10 (9.2)	2 (1.9)
SD	98 (45.8)	54 (49.5)	44 (41.9)
PD	19 (8.9)	7 (6.4)	12 (11.4)

a 2-sided Exact Binomial 95% CI.
b Duration of response is calculated as the date of the first documented response to the date of the first documented disease relapse, progression or death due to any cause, whichever occurs first. Percentile was estimated using Kaplan-Meier method.
c Percentages are based on the number of R/R AML subjects in each group.
Source: 'Summary of clinical efficacy', table 23, page 103

Table eff 10. IRAC best responses (FAS for R/R AML + enasidenib 100 mg QD)

	Combined Phase 1/2 100 mg (N = 214)	**Phase 1 100 mg (N = 109)**	**Phase 2 100 mg (N = 105)**
CR Rate (n [%]) (95% CI)[a]	41 (19.2) (14.1, 25.1)	23 (21.1) (13.9, 30.0)	18 (17.1) (10.5, 25.7)
KM Median **Duration of CR** (months)[b] (95% CI)	7.4 (5.6, 11.5)	9.7 (5.4, 24.0)	6.5 (4.6, 9.2)
CR+CRi/CRp Rate (n [%]) (95% CI)[a]	59 (27.6) (21.7, 34,1)	31 (28.4) (20.2, 37.9)	28 (26.7) (18.5, 36.2)

KM Median **Duration of CR+CRi/CRp** (months)[b] (95% CI)	6.5 (5.1, 7.4)	5.5 (2.6, 11.5)	6.5 (4.6, 9.2)
ORR (CR+CRi+CRp+PR+MLFS)[c] (n [%]) (95% CI)[a]	76 (35.5) (29.1, 42.3)	43 (39.4) (30.2, 49.3)	33 (31.4) (22.7, 41.2)
KM Median **Duration of ORR** (months)[b] (95% CI)	5.6 (3.7, 6.5)	5.1 (1.9, 6.6)	6.5 (4.6, 9.2)

a 2-sided Exact Binomial 95% CI.
b Duration of response is calculated as the date of the first documented response to the date of the first documented disease relapse, progression or death due to any cause, whichever occurs first. Percentile was estimated using Kaplan-Meier method.
c Percentages are based on the number of R/R AML subjects in each group.
Source: 'Summary of clinical efficacy', table 27, page 107

Table eff 11. Sensitivity analyses for investigator assessed responses (Evaluable Analysis Set for R/R AML + enasidenib 100 mg QD)

	Combined Phase 1/2 100 mg (N = 177)	**Phase 1 100 mg (N = 93)**	**Phase 2 100 mg (N = 84)**
CR Rate (n [%]) (95% CI)[a]	37 (20.9) (15.2, 27.6)	20 (21.5) (13.7, 31.2)	17 (20.2) (12.3, 30.4)
CR+CRi/CRp Rate (n [%]) (95% CI)	57 (32.2) (25.4, 39.6)	28 (30.1) (21.0, 40.5)	29 (34.5) (24.5, 45.7)
ORR (CR+CRi+CRp+PR+MLFS) (n [%]) (95% CI)[b]	76 (42.9) (35.5, 50.6)	41 (44.1) (33.8, 54.8)	35 (41.7) (31.0, 52.9)

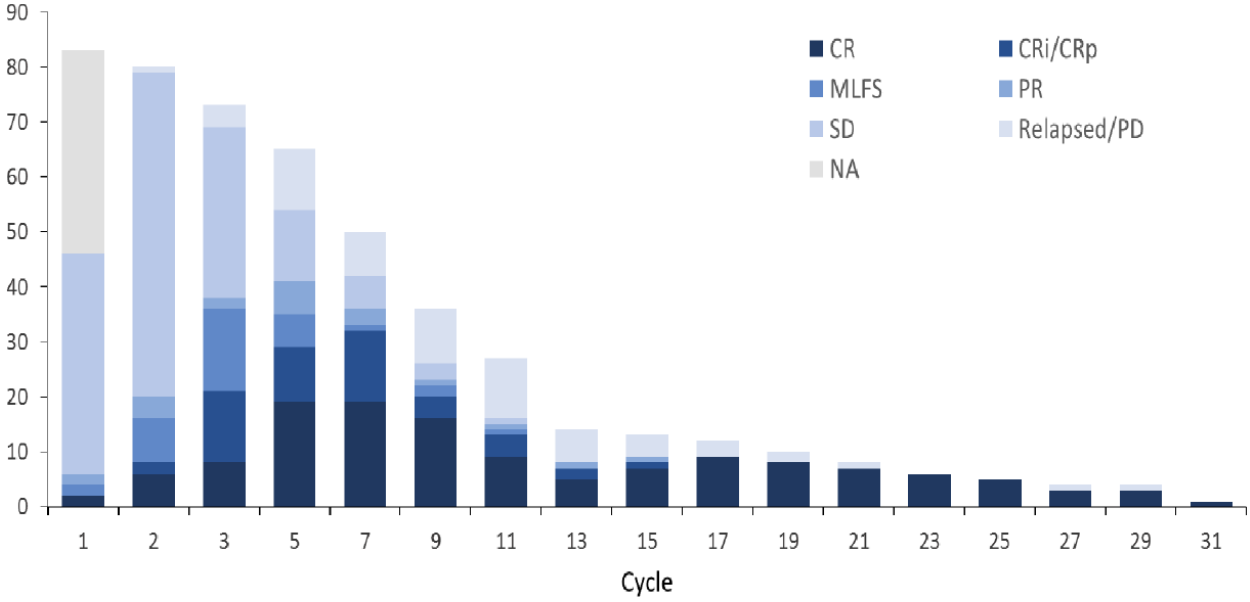
a 2-sided Exact Binomial 95% CI.
b Percentages are based on the number of R/R AML subjects in each group.
Source: 'Summary of clinical efficacy', table 28, page 108

Table eff 12. Sensitivity analyses for Duration of ORR (FAS for R/R AML + enasidenib 100 mg QD)

Combined Phase 1/2 100 mg (N = 214)	**Phase 1 100 mg (N = 109)**	**Phase 2 100 mg (N = 105)**
Median DoR (95% CI) [a]		
5.6 (3.8, 7.4)	5.3 (3.3, 9.7)	6.5 (3.7, 7.4)
Median DoR (95% CI) [b]		
5.6 (3.7, 7.4)	5.6 (3.1, 16.3)	5.6 (3.7, 7.4)
Median DoR (95% CI) [c]		
5.3 (3.7, 6.5)	5.3 (3.1, 8.8)	4.6 (2.8, 6.7)

a Subjects with 2 or more consecutive missing response assessments prior to an event and/or subjects with subsequent anticancer therapies prior to an event were considered as events at the event date by ignoring the missing assessments and subsequent anticancer therapies.
b Subjects who underwent HSCT were censored at the last adequate assessment prior to HSCT.
c Includes unconfirmed progressive disease.
Duration of response was calculated as the date of the first documented response to the date of the first documented disease elapse, progression or death due to any cause, whichever occurred first. Percentile was estimated using Kaplan-Meier Method.
Source: 'Summary of clinical efficacy', table 29, page 109

Figure eff 03. Response by cycle (FAS for R/R AML + enasidenib 100 mg QD)



Source: Figure 14.2.24.7

Table eff 13. Time to First and Best Response, DoR, and Treatment Duration by Best Response (FAS for R/R AML + enasidenib 100 mg QD)

	Total R/R AML, 100 mg QD (N = 214)					
	CR (n = 42)	**CRi/CRp (n = 20)**	**CR+ CRi/CRp (n = 62)**	**PR (n = 9)**	**MLFS (n = 12)**	**ORR (n = 83)**
Median Time to First Response (months)[a] (Min, Max)	1.9 (0.5, 9.2)	1.8 (0.6, 7.3)	1.9 (0.5, 9.2)	3.7 (0.9, 5.6)	1.4 (0.6, 9.4)	1.9 (0.5, 9.4)
Median Time to Best Response (months)[b] (Min, Max)	3.7 (0.7, 14.7)	1.9 (1.0, 9.2)	3.7 (0.7, 14.7)	3.7 (0.9, 5.6)	1.4 (0.6, 9.4)	3.7 (0.6, 14.7)
KM Median Duration of Response (months) (95% CI)	7.4 (6.5, 16.3)	4.6 (1.9, NA)	6.7 (5.3, 9.7)	3.8 (0.8, 5.8)	1.6 (0.5, 2.6)	5.6 (3.8, 7.4)
Median Duration of Treatment (months) (Min, Max)	10.7 (3.5, 34.1)	6.1 (2.1, 15.8)	8.8 (2.1, 34.1)	6.5 (1.8, 16.1)	5.6 (1.8, 17.6)	7.4 (1.8, 34.1)

Source: 'Summary of clinical efficacy', table 30, page 111

For CR, the median time to first response was 1.9 months and the median time to best response was 3.7 months, indicating that some subjects met the criteria for non-CR responses prior to achieving CR. Consistent with this, of the subjects who achieved a best response of CR, 19.0% (8/42) achieved CR by Cycle 3, 59.5% (25/42) achieved CR by Cycle 5, and 83.3% (35/42) achieved CR by Cycle 7. For subjects with a best response of CR+CRi/CRp, 30.6% (19/62) achieved this response by Cycle 3, 62.9% (39/62) by Cycle 5, and 85.5% (53/62) by Cycle 7.

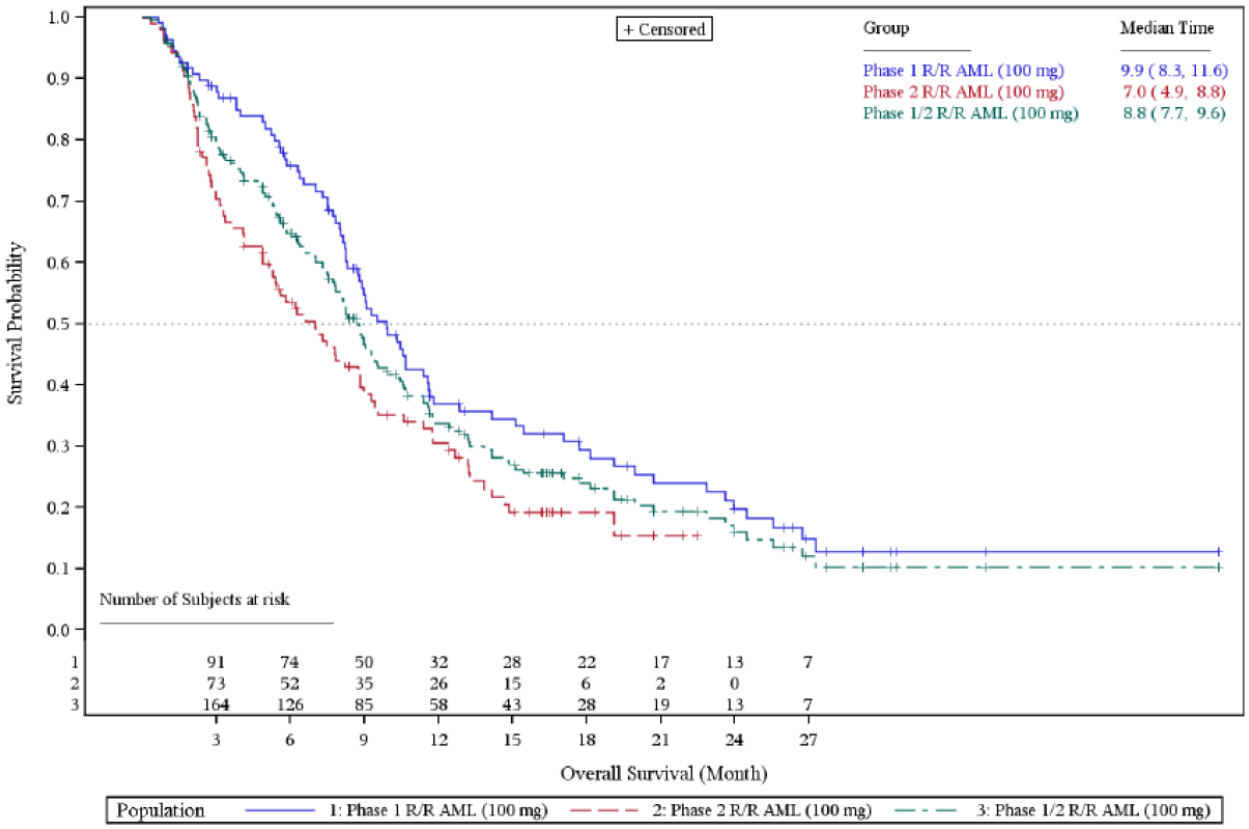
Overall survival (OS)

Table eff 16. Overall Survival (FAS for R/R AML + enasidenib 100 mg QD)

Overall Survival (OS) [a]	Combined Phase 1/2 100 mg (N = 214)	Phase 1 100 mg (N = 109)	Phase 2 100 mg (N = 105)
Number (%) of Death Events	157 (73.4)	78 (71.6)	79 (75.2)
Number (%) Censored [b]	57 (26.6)	31 (28.4)	26 (24.8)
Median OS in months (95% CI)	8.8 (7.7, 9.6)	9.9 (8.3, 11.6)	7.0 (4.9, 8.8)

a Overall Survival was calculated as the time from the first dose to the date of death due to any cause. Percentile was estimated using Kaplan-Meier method.
b Subjects alive were censored at the last date known to be alive or a pre-specified data cutoff date. Subjects who only had a baseline record were censored at the first dose date.
Source: 'Summary of clinical efficacy', table 23, page 103

Figure eff 04. Kaplan-Meier Curve for Overall Survival (FAS for R/R AML + enasidenib 100 mg QD)



Source: Figure 14.2.14.13.1

OS was longest for subjects who achieved CR with a median duration of OS of 22.9 months (95% CI: 13.2, NE). The duration of OS was shorter for non-responders (best response of SD, PD or NE) with a median duration of OS of 5.6 months (95% CI: 4.1, 7.3). Median duration of OS for subjects with CR+CRi/CRp was 18.2 months (95% CI: 11.8, 25.6).

Haematopoietic stem cell transplantation (HSCT)

19/214 (8.9%) of the patient in the combined phase 1/2 R/R AML population who received 100 mg enasidenib daily were able to discontinue enasidenib and to proceed to directly receive allogeneic HSCT. This included 10 subjects from phase 1 and 9 subjects from phase 2.

Table eff 17. Investigator-assessed best response to enasidenib in R/R AML subjects who underwent allogeneic HSCT following enasidenib treatment (FAS for R/R AML + enasidenib 100 mg QD)

	Subjects Who Underwent Allogeneic HSCTfollowing Enasidenib Treatment			Overall Combined Phase 1 + 2 100 mg (N=214)
	Phase 1 100 mg (N = 10)	Phase 2 100 mg (N = 9)	Combined Phase 1/2 100 mg (N = 19)	
Age				
Median (Min, Max)	57.0 (19.0, 73.0)	60.0 (32.0, 70.0)	58.0 (19.0, 73.0)	68.0 (19.0, 100.0)
Prior MDS				
n (%)	0	3 (33.3)	3 (15.8)	46 (21.5)
Primary Refractory				
n (%)	6 (60.0)	2 (22.2)	8 (42.1)	84 (39.3)
R/R AML Subgroups (n, %) [a]				
Overall	10 (100.0)	7 (77.8) [d]	17 (89.5) [d]	196 (91.6) [e]
Relapse after allogeneic transplantation	2 (20.0)	0	2 (11.8)	29 (14.8)
Second or later relapse	0	0	0	27 (13.8)
Refractory to initial induction or re-induction treatment	6 (60.0)	3 (42.9)	9 (52.9)	64 (32.7)
Relapse within 1 year of initial treatment [b]	2 (20.0)	3 (42.9)	5 (29.4)	55 (28.1)
Failed 2 or more cycles of first line therapy [c]	1 (10.0)	1 (14.3)	2 (11.8)	57 (29.1)
Number of Prior Anticancer Regimens (n [%])				
1	8 (80.0)	2 (22.2)	10 (52.6)	101 (47.2)
2	2 (20.0)	4 (44.4)	6 (31.6)	65 (30.4)
3	0	1 (11.1)	1 (5.3)	30 (14.0)
4	0	1 (11.1)	1 (5.3)	12 (5.6)
≥ 5	0	1 (11.1)	1 (5.3)	6 (2.8)
Prior Allogeneic HSCT				
n (%)	2 (20.0)	0	2 (10.5)	29 (13.6)

Source: 'Summary of clinical efficacy', table 40, page 131

Table eff 18. Investigator-assessed best response to enasidenib in R/R AML subjects who underwent allogeneic HSCT following enasidenib treatment (FAS for R/R AML + enasidenib 100 mg QD)

	Combined Phase 1/2 100 mg (N = 19)	Phase 1 100 mg (N = 10)	Phase 2 100 mg (N = 9)
Best Response (n %)			
CR	6 (31.6)	3 (30.0)	3 (33.3)
CRi/ CRp	8 (42.1)	3 (30.0)	5 (55.6)
PR	2 (10.5)	1 (10.0)	1 (11.1)
MLFS	1 (5.3)	1 (10.0)	0
SD	1 (5.3)	1 (10.0)	0
NE	1 (5.3)	1 (10.0)	0

Source: 'Summary of clinical efficacy', table 41, page 132

Table eff 19. Post-transplant OS of R/R AML subjects who Underwent allogeneic HSCT following enasidenib treatment (FAS for R/R AML + enasidenib 100 mg QD)

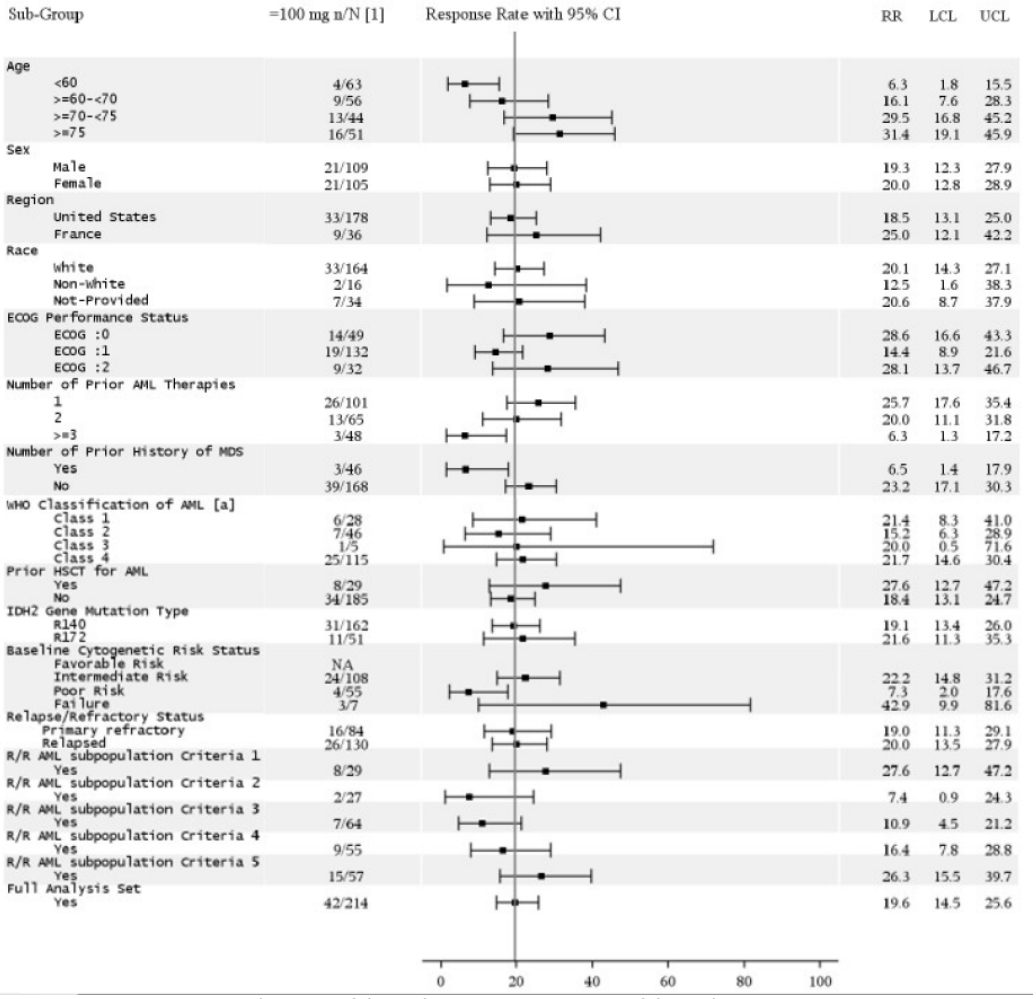
	Combined Phase 1/2 100 mg (N = 19)	Phase 1 100 mg (N = 10)	Phase 2 100 mg (N = 9)
Duration of OS from the Date of First Dose of Enasidenib (months)[a]			
Median (95% CI)	23.6 (10.6, NA)	23.6 (8.8, NA)	NA (9.0, NA)
Post-Transplant Duration of OS (months)[b]			
Median (95% CI)	16.0 (5.1, NA)	16.0 (1.7, NA)	NA (4.0, NA)
3 Months Post Transplant	93.8	85.7	100.0
12 Months Post Transplant	53.6	57.1	50.0

a OS is calculated as the time from the first dose to the date of death due to any cause.
b OS after HSCT is calculated as the time from transplant to the date of death due to any cause.
Source: 'Summary of clinical efficacy', table 42, page 133

Subgroup analyses

Subgroup analyses of key efficacy endpoints (CR, CR+CRi/CRp, ORR and OS) for R/R AML subjects who received a total daily dose of 100 mg in the combined Phase 1/2 population were performed by baseline demographic characteristics (i.e., age, gender, race, region) and by baseline disease characteristics (i.e., baseline ECOG PS, number of prior AML therapies, prior history of MDS, WHO classification of AML, prior HSCT for AML, IDH2 gene mutation type, baseline cytogenetic risk status, R/R status, and R/R AML subtypes).

Figure eff 05. Forest plot of CR rate baseline characteristics (FAS for R/R AML + enasidenib 100 mg QD)



RR = response rate; LCL = lower confidence limit; UCL = upper confidence limit

a Class 1: AML with Recurrent Genetic Abnormalities, Class 2: AML with myelodysplasia-related changes, Class 3: therapy related myeloid neoplasms, Class 4: AML not otherwise specified.

Note: The vertical line indicates the CR rate in the overall FAS population (bottom row).

[1] n = number of responders (CR). N = number of subjects in each subgroup.

R/R AML subpopulation criteria:

Criterion 1: subjects who relapse after allogeneic transplantation;
Criterion 2: subjects in second or later relapse;
Criterion 3: subjects who are refractory to initial induction or re-induction treatment;
Criterion 4: subjects who relapse within 1 year of initial treatment, excluding subjects with favourable-risk status according to NCCN Guidelines (NCCN v1.2015); Favourable-risk cytogenetics: inv(16), +(16;16), t(8;21), t(15;17)
Criterion 5: subjects who have failed 2 or more cycles of first line therapy (consisting of an intermediate intensity chemotherapy, hypomethylating agent, or low dose cytarabine).

Source: Figure 14.2.22.3

Table eff 20. OS by baseline characteristics (FAS for R/R AML + enasidenib 100 mg QD)

Baseline Variable	Subgroup	Combined Phase 1/2 100 mg (N = 214)		Phase 1 100 mg (N = 109)		Phase 2 100 mg (N = 105)	
		N[a]	Median (95% CI)	N[a]	Median (95% CI)	N[a]	Median (95% CI)
Age (years)	< 60	63	9.0 (7.0, 12.8)	38	11.6 (8.8, 17.1)	25	6.3 (2.2, 8.2)
	≥ 60 < 70	56	6.6 (4.9, 9.0)	22	9.5 (5.0, 23.9)	34	5.2 (2.3, 7.8)
	≥ 70 < 75	44	10.7 (8.9, 14.9)	23	9.9 (7.0, 19.1)	21	12.4 (7.5, 14.9)
	≥ 75	51	7.5 (4.9, 10.3)	26	7.7 (5.6, 10.5)	25	7.0 (3.3, 13.2)

Gender	Male	109	8.3 (6.3, 9.0)	46	8.8 (6.3, 10.7)	63	7.5 (4.9, 9.0)
	Female	105	9.3 (7.8, 11.6)	63	10.7 (8.8, 15.1)	42	5.8 (3.2, 9.6)
Race	White	164	8.9 (7.5, 10.5)	86	9.5 (8.1, 11.4)	78	7.8 (4.1, 10.6)
	Non-White	16	7.4 (3.6, 19.9)	9	17.1 (2.0, NA)	7	5.2 (1.9, 8.8)
	Not Provided	34	8.8 (5.8, 11.6)	14	10.4 (8.0, 23.9)	20	6.2 (4.9, 9.3)
Region	USA	178	8.2 (7.3, 9.4)	92	8.9 (7.7, 10.6)	86	7.3 (4.1, 9.0)
	France	36	11.6 (8.0, 17.7)	17	23 (9.1, NA)	19	6.6 (4.9, 9.3)
EGOG Performance Status	0	49	9.4 (8.2, 23.9)	25	9.0 (7.7, 23.9)	24	14.2 (5.4, NA)
	1	132	8.8 (7.0, 9.9)	68	10.3 (8.3, 14.2	64	5.8 (3.2, 7.8)
	2	32	5.8 (3.0, 10.5)	16	7.8 (1.5, 11.6)	16	4.6 (2.2, 11.7)
Prior AML Therapies	1	101	11.8 (8.3, 15.4)	59	15.4 (9.0, 22.9)	42	8.2 (5.3, 12.7)
	2	65	7.8 (5.8, 9.1)	27	8.3 (6.3, 10.7)	38	7.3 (3.3, 9.6)
	≥ 3	48	7.0 (4.9, 8.8)	23	9.3 (5.9, 10.3)	25	4.9 (2.1, 7.8)
Prior MDS	Yes	46	7.0 (4.9, 8.3)	17	8.0 (4.0, 9.0)	29	6.2 (2.8, 8.8)
	No	168	9.3 (8.2, 11.4)	92	10.5 (8.9, 14.2)	76	7.3 (4.9, 9.4)
WHO Classification of AML [b]	Class N1	28	7.3 (5.6, 10.7)	7	7.3 (1.8, 9.0)	21	8.8 (4.9, 13.8)
	Class N2	46	7.8 (4.9, 9.9)	27	8.3 (5.6, 10.6)	19	4.9 (2.3, 7.8)
	Class N3	5	2.2 (0.4, NA)	1	NA	4	1.5 (0.4, NA)
	Class N4	115	10.3 (8.2, 12.4)	62	11.8 (9.3, 19.9)	53	7.5 (4.1, 11.4)
Prior HSCT	Yes	29	5.9 (2.3, 8.8)	12	11.6 (5.9, 27.3)	17	2.3 (1.9, 4.9)
	No	185	9.0 (7.8, 10.5)	97	9.3 (8.2, 11.4)	88	7.8 (5.6, 11.4)
IDH2 Gene Mutation	R140	162	8.2 (7.0, 9.3)	83	9.0 (8.1, 11.6)	79	5.6 (4.1, 8.8)
	R172	51	10.6 (7.5, 12.7)	25	10.7 (7.5, 23.6)	26	9.0 (4.9, 12.7)
Cytogenetic Risk	Intermediate	108	9.3 (8.2, 11.6)	51	9.9 (8.3, 12.8)	57	8.8 (4.9, 12.4)
	Poor	55	7.0 (5.0, 8.3)	29	8.3 (5.9, 11.8)	26	4.3 (2.2, 7.0)
R/R AML Type	Primary Refractory	84	9.9 (7.5, 13.8)	48	9.9 (8.0, 17.1)	36	9.3 (5.3, 13.8)
	Relapsed	130	8.1 (7.0, 9.3)	61	9.5 (8.1, 11.6)	69	5.6 (3.2, 7.8)
R/R AML Subpopulation [c]	Criterion 1	29	5.9 (2.3, 8.8)	12	11.6 (5.9, 27.3)	17	2.3 (1.9, 4.9)
	Criterion 2	27	5.9 (4.1, 8.8)	14	7.3 (4.9, 9.5)	13	4.9 (1.9, 8.8)
	Criterion 3	64	8.9 (7.0, 12.4)	36	9.0 (8.0, 17.1)	28	7.3 (3.6, 12.4)
	Criterion 4	55	7.8 (5.9, 9.3)	26	9.3 (7.0, 15.1)	29	5.8 (2.2, 8.8)
	Criterion 5	57	8.8 (5.8, 11.7)	25	9.9 (5.6, 10.7)	32	8.8 (4.1, 13.2)

a N = number of subjects in subgroup category

b WHO classification: N1 = AML with recurrent genetic abnormalities; N2 = AML with myelodysplasia-related changes; N2 = Therapy related myeloid neoplasms; N4 = AML not otherwise specified

c Subpopulation criteria:

Criterion 1: subjects who relapse after allogeneic transplantation;
Criterion 2: subjects in second or later relapse;
Criterion 3: subjects who are refractory to initial induction or re-induction treatment;
Criterion 4: subjects who relapse within 1 year of initial treatment, excluding subjects with favourable-risk status according to National Comprehensive Cancer Network (NCCN) Guidelines (NCCN v1.2015). Favourable-risk cytogenetics: inv(16), +(16;16), t(8;21), t(15;17);
Criterion 5: subjects who have failed 2 or more cycles of first line therapy (consisting of an intermediate intensity chemotherapy, hypomethylating agent, or low dose cytarabine).

Source: 'Summary of clinical efficacy', table 43, page 140

Summary of main efficacy results

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table eff 21. Summary of efficacy for trial AG221-C-001

Title: A Phase 1/2, Multicentre, Open-Label, Dose Escalation and Expansion, Safety, PK, PD, and Clinical Activity Study of Orally Administered Enasidenib (AG-221) In Subjects With Advanced Haematologic Malignancies With an IDH2 Mutation	
Study identifier	EudraCT number: 2013-001784-23; ClinicalTrials.gov Id: NCT01915498

Design	uncontrolled, open-label, multicentre		
	Study start date: Data cut-off: Status:		20 Sep 2013 (phase 1); 25 Jun 2015 (phase 2) 01 Sep 2017 Full CSRs completed for 01 Sep 2017, study ongoing (n=54), treatment ongoing (n=16)
Hypothesis	Exploratory		
Treatments group	Enasidenib 100mg daily (R/R AML)		Enasidenib 100 mg daily [population included in current MAA: n= 214 IDH2 mutated R/R AML patients (phase1: n=109; phase 2: n= 105)] [overall population included into the trial: n=345 patients with advanced IDH2 mutated haematologic malignancies and diverse enasidenib doses (phase 1: n=239; phase 2: n=106)]
Endpoints and definitions	Key efficacy endpoints	CR rate DoCR	complete remission rate duration of complete remission
	Other efficacy endpoints	CR/CRi/CRp rate OS	CR rate including incomplete haematologic recovery based on neutrophils (CRi) and incomplete platelet recovery (CRp) overall survival
Database lock	study ongoing		

Results and Analysis

Analysis description	**exploratory analyses**	
Analysis population	FAS [full analysis set: all (R/R AML) subjects who were enrolled and received at least one dose of treatment]	
Descriptive statistics and estimate variability	Treatment group	Enasidenib 100mg daily (R/R AML)
	Number of subjects	214
	CR rate (n [%])	42 (**19.6**)
	95% CI	(14.5, 25.6)
	DoCR (months)	**7.4**
	95% CI	(6.5, 16.3)
	CR+CRi/CRp (n [%])	62 (29.0)
	95% CI	(23.0, 35.5)
	Duration of CR+CRi/CRp (months)	5.6
	95% CI	(3.8, 7.4)
	OS [median; months]	8.8
	95% CI	(7.7, 9.6)
Notes	Study AG221-C-001 is an uncontrolled open-label first-in-human phase 1/2 study being used as single pivotal evidence in an MAA for CMA. The study was amended 7 times. Amendments included modifications of the study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size (list incomplete). In conclusion, data provided from study AG221-C-001 are exploratory, analyses performed are descriptive.	

External / historical control

Considering that the AG221-C-001 study is a single arm study without an active comparator arm, the applicant provides a comparison of clinical effectiveness of enasidenib in the R/R AML with historical data by using 3 methods:

- a systematic review of published literature and
- a comparison of the AG221-C-001 data versus AML registry data collected in R/R AML patients with an IDH2 mutation treated with conventional treatments in a real-world setting (the mentioned registries being the AMLSG (Germany) and PETHEMA (Spain)).
- A propensity score matching analysis of study AG221-C-001 vs French Chart Review and vs AMLSG

Literature review (published literature R/R AML irrespective of IDH mutational status)

Following the identification of R/R AML publications, a comprehensive clinical review of each publication was undertaken to identify:

- Well controlled studies with a significant number of R/R AML subjects that would allow for a meaningful comparison to the Study AG221-C-001 R/R AML population irrespective of IDH2 status.
- Studies in AML subjects with an IDH2 mutation, irrespective of the line of therapy.

The published literature search identified 7 studies that met the criteria for historical control selection. Of these, 3 were in an R/R AML population with the IDH2 mutation. A side by side comparison of the 7 studies in terms of baseline characteristics and efficacy results against Study AG221-C-001 is provided in Table eff 22.

Table eff 22: Cross Study Comparison of AG221-C-001 Combined Phase 1/2 Baseline Characteristics, Efficacy and Safety Data versus R/R AML Historical Controls

IDH2 Status	IDH2 mutated				IDH2 mutation status unknown			
Study/ Publication	**AG221-C-001[a] Phase 1/2**	**DiNardo, 2015**	**Paschka, 2016[k]**	**Bertoli, 2016**	**Roboz, 2014**	**Faderl, 2012 CLASSIC I**	**Ravandi, 2015 VALOR**	**Giles, 2005**
AML Population	1º refractory; relapse within 1 yr; ≥2nd relapse; relapse after HSCT	IDH2 mutated; induction (initial diagnosis), Salvage-1, ≥ Salvage-2	IDH2 mutated; First salvage after first relapse	IDH2 mutated, 1º refractory, first relapse after intensive chemotherapy	1º refractory/ relapse after 2-3 prior induction/ re-induction	1º refractory or first relapse after ≤ 2 inductions	1º refractory or first relapse	Second salvage
Study Phase	Combined Phase 1/2 Non-randomized clinical trial	Retrospective Observational Study	Retrospective Observational Study	Retrospective Observational Study	Phase 3 Clinical Trial	Phase 3 Clinical Trial	Phase 3 Clinical Trial	Retrospective Observational Study
Treatment	Enasidenib (AG-221) 100 mg daily	HiDAC, HMAs, LDAC, Other	HiDAC, AlloSCT	intensive chemotherapy	HiDAC, MEC, FLAG/FLAG-Ida, LDAC, HMA, Hydroxyurea, SC	HiDAC	HiDAC	HiDAC, SDAC, AlloSCT, Non-AC regimens, Phase 1/2 agents, Other
N	214	Salvage 1 n = 18, Salvage ≥ 2 n =19	98	23	190	158j	355j	594
Median age (yrs) (range)	68 (19-100)	66h (22-90)	NR	NR	63 (19-83)	67 (55-86)	63 (18-82)	50 (13-83)
ECOG (%)								
0	22.9	NR	NR	NR	28	30	41	18
1	61.7				50	58	46	53
2	15.0				20	11	14	29[b]
Cytogenetic risk (%)								
Favourable	0	0	NR	NR	5	6	4	NR
Intermediate	50.5c	81			45	53	65	

IDH2 Status	IDH2 mutated				IDH2 mutation status unknown			
Study/ Publication	AG221-C-001[a] Phase 1/2	DiNardo, 2015	Paschka, 2016[k]	Bertoli, 2016	Roboz, 2014	Faderl, 2012 CLASSIC I	Ravandi, 2015 VALOR	Giles, 2005
Adverse	28.7c	15h			47	39	31	
No. prior regimens (%)								
1	52.3	17	100	100	9	100	100	0
2	24.8	18g	0	0	67	0	0	100
≥3	23.0	NR	0	0	24	0	0	NR
CR (%)	19.6	NR	52	52	10.5e	18i	16	13
CR/CRi (%)	29.0	50d/26g	NR	NR	21.0	22.9	19.0f	19.0
PR (%)	4.2	NR	NR	NR	0	1	NR	< 1
Duration of CR (months)	7.4	NR	NR	NR	NE	NR	NR	7.0
OS Origin Date	Date of 1st treatment dose	Date of presentation (inclusion)	Date of initial diagnosis	Date of relapse	Date of start of treatment	Date of randomization	Date of randomization	Date of start of the 2nd salvage treatment
OS (months) (median)	8.8a	11.1d/5.9g 9.9d,h/4.7g,l	13.1	11	3.3	6.3	6.1	1.5

AC= cytarabine; AlloSCT= allogeneic stem cell transplant; CR = complete response; CRi = complete response with incomplete hematologic recovery; CRp = complete response with incomplete platelet recovery; ECOG = Eastern Cooperative Oncology Group; FLAG/FLAG-Ida = fludarabine, cytarabine, granulocyte colony-stimulating factor with or without idarubicin; HiDAC = high-dose cytarabine; HMA = hypomethylating agents; HSCT = hematopoietic stem cell transplant; LDAC = low-dose cytarabine; MEC = mitoxantrone, etoposide, cytarabine; NE=not evaluable; NR=not reported; OS = overall survival; PLT=platelet; PR = partial response; RBC=red blood cell; SC= supportive care; SDAC = standard dose cytarabine; yr = year.

a 01 Sep 2017 data cutoff.
b Includes ECOG ≥2.
c Percentage based on non-missing cytogenetic results.
d Salvage 1 subjects (n= 18)
e Intent-to-treat population (12% by efficacy evaluable population).
f CR+CRi+CRp.
g ≥ Salvage 2 subjects (n = 19).
h Data for all 106 IDH2 subjects. Data for subject in relapse/salvage 1 or 2 was not reported.
i of 157 subjects.
j Placebo + cytarabine arm
k Retrospective review by the AML Study Group (AMLSG)
l OS for patients ≥ 60 years old who likely did not receive intensive chemotherapy per institutional practice (salvage 1: n = 14; salvage 2: n = 7; personal communication).

Registry data (R/R AML with IDH2 mutation)

In order to put Study AG221-C-001 into the context of the therapeutic landscape, the results were also compared with historical efficacy data collected in a comparable population (according to the inclusion criteria of Study AG221-C-001) from registries/academic groups (referred to as registries). Efforts were made to identify registries in both the EU and North America that had R/R AML patients treated with conventional treatments.

The applicant has compared efficacy data from AG221-C-001 retrospectively with aggregated data from subsets of patients from the AML S Bio Registry and the PETHEMA Registry that met the key eligibility criteria of the AG221-C-001 study.

The baseline definition that was used in Study AG221-C-001 (the starting date of the experimental treatment [i.e., date of first enasidenib dose in the study]), could not be applied to the historical data, since there is no experimental treatment. As such, baseline definition for historical data was defined as the date of last R/R event. This is considered to be a more conservative approach than using start of therapy for relapse, as relapse occurs prior to starting therapy for that relapse.

A total of 207 patients from the AMLSG registry and 29 from the PETHEMA registry were identified to meet inclusion criteria and have been included in this comparison. All patients were positive for the IDH2 mutation and had confirmed AML with relapsed or refractory disease status.

Overall, the distribution of the baseline characteristics known to impact the prognosis of R/R AML (e.g., age, number of prior AML therapies, prior MDS, cytogenetic risk status) suggest a more favourable prognosis overall for the AMLSG cohort than that of the AG221-C-001 study. Age and cytogenetic risk status were also more favourable for the PETHEMA cohort, while the distribution of number of prior AML therapies was more favourable for Study AG221-C-001. However, the small sample size of the PETHEMA cohort and wide confidence intervals limit this comparison.

Patients in both the AMLSG and PETHEMA cohorts were younger than subjects in Study AG221-C-001 (respective median age 60.6 and 56.0 years, respectively, versus 68.0 years). In addition, the proportion of patients below the age 65 was higher in both registry cohorts (63% and 72%, respectively, versus 40%).

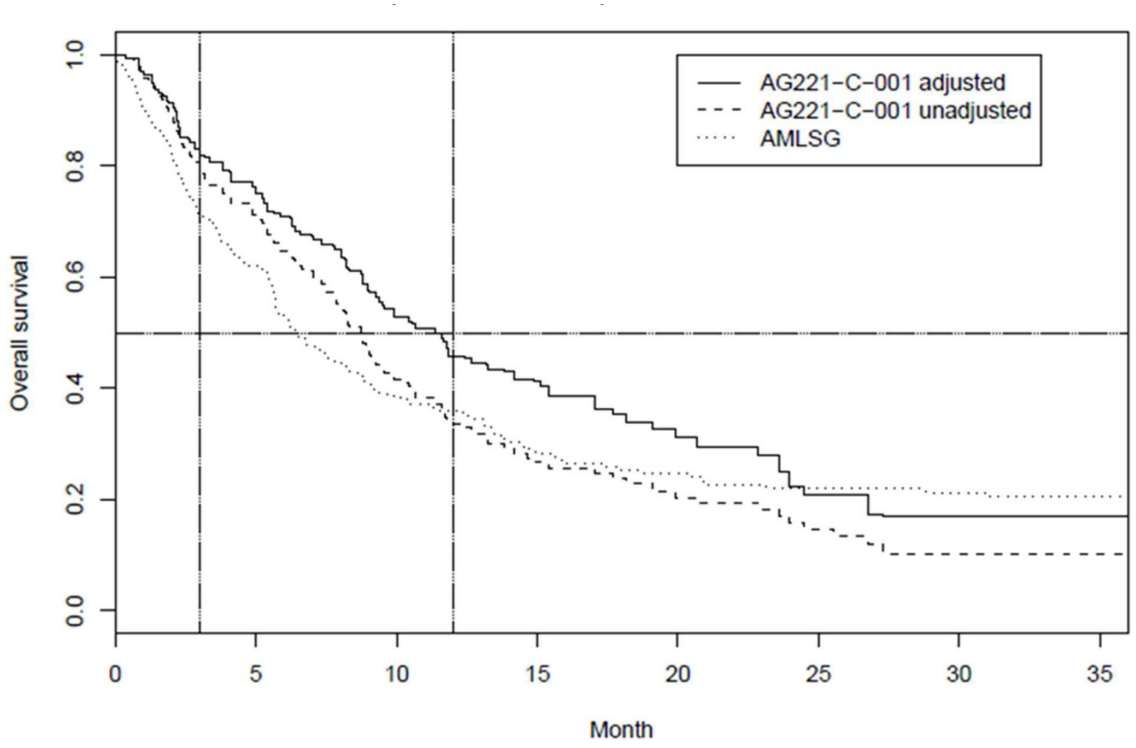
Furthermore, imbalances between the AMLSG cohort and the AG221-C-001 study population in the distribution of additional important prognostic factors (number of prior treatments and prior MDS) was also observed, and thus an adjustment was performed to allow for a more appropriate overall survival comparison. This adjustment was repeated with the PETHEMA data. The AMLSG cohort that matched the Study AG221-C-001 eligibility criteria demonstrated a median OS of 6.4 months (95% CI: 5.7, 8.3) as compared with the 8.8 months (95% CI: 7.7, 9.6) observed in the Phase 1/2 R/R AML population from the Study AG221-C-001. After applying the adjustment to equitably distribute the prognostic factors (age, number of prior AML treatments, and prior history of MDS) between Study AG221-C-001 and the AMLSG cohort, the median OS of the AG221-C-001 population was extended to 11.4 months (Table eff 23 and Figure eff 6).

Table eff 23: Overall Survival Kaplan Meier Analyses of the AMLSG Cohort and Study AG221-C-001

Parameter	**AMLSG (n= 207)**	**AG221-C-001 Unadjusted (N = 214)**	**AG221-C-001 Adjusted (N = 214)**
Number of deaths	159	157	134
Median OS (months) 95% CI	6.4 (5.7, 8.3)	8.8 (7.7; 9.6)	11.4 (9.3, 14.2)

3-month survival rate (%) (95% CI)	70.9 (64.7, 77.1)	79.6 (74.2, 85.1)	82.8 (77.6, 87.9)
12-month survival (%) (95% CI)	36.1 (29.4, 42.8)	33.7 (26.9, 40.4)	45.7 (38.5, 53.0)

Figure eff 6: Kaplan- Meier Curves for Overall Survival for the AMLSG Cohort, Study AG221-C-001 Adjusted and Unadjusted

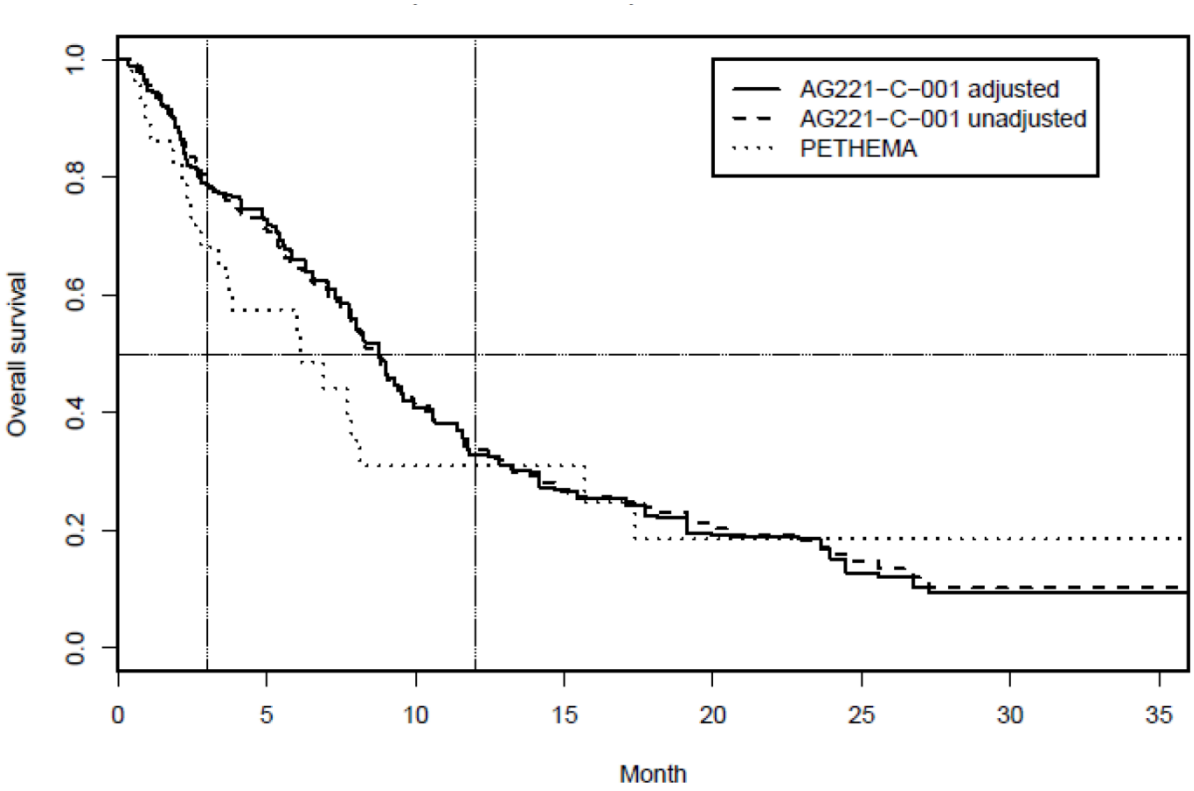


Similar results were obtained from the PETHEMA cohort, which had a median OS of 6.1 months (95% CI: 3.3, 8.2). After applying the adjustment described above to equitably distribute the prognostic factors between Study AG221-C-001 and the PETHEMA cohort, the median OS of the AG221-C-001 population remained 8.8 months (Table eff 24 and Figure eff 7). It is possible that the small sample size of the PETHEMA cohort and subsequent large confidence intervals for both baseline patient and disease characteristics may minimize the influence of imbalances with the AG221-C-001 population on the adjustment.

Table eff 24: Overall Survival Kaplan Meier Analyses of the PETHEMA Cohort and Study AG221-C-001

Parameter	**PETHEMA (N = 29)**	**AG221-C-001 (N = 214)**	**AG221-C-001 Adjusted**
Number of deaths	21	157	160
Median OS (months) 95% CI)	6.1 (3.3, 8.2)	8.8 (7.7, 9.6)	8.8 (7.8, 9.5)
3-month survival rate (%) (95% CI])	68.1 (50.9, 85.3)	79.6 (74.2, 85.1)	78.3 (72.7, 83.8)
12-month survival rate (%) (95% CI)	30.9 (12.5, 49.3)	33.7 (26.9, 40.4)	31.8 (25.1, 38.5)

Figure eff 7: Kaplan-Meier Curves for Overall Survival for the PETHEMA Cohort, Study AG221-C-001 Adjusted and Unadjusted



Propensity score matching analysis: AG-221-C-001 vs French Chart Review Study and vs AMLSG

The applicant conducted a propensity score matching analysis to put OS observed in Study AG221-C-001 into the context of the therapeutic landscape by comparing the results with real-world efficacy data collected in a comparable population (according to the inclusion criteria of Study AG221-C-001) from a similar group of patients treated with SoC from the French Chart Review Study and a similar group of patients treated with SoC from the AMLSG Bio Registry.

The France Chart review was a retrospective, observational, multi-centre, chart-review study in patients with R/R AML and an IDH2 mutation. The chart review was carried out at nine centres in France that had in-patient diagnostic and treatment facilities for patients with AML, belonged to a network of oncologists or haematologists who treat patients with R/R AML, had been operational and treating AML patients for at least 24 months, and had clinical records available for review.

Overall, 133 subjects were screened and 104 enrolled (the main reasons for exclusion being patient not relapsed/refractory, previous exposure to enasidenib and clinical data collected outside the considered study period). Clinical data were available for 103/104 (FAS). Median age was 65 years (range 33 – 87 years), 57% of subjects were male and 43% female. Approximately one-third of subjects had cardiac or cerebrovascular disease at baseline. A higher percentage of subjects had only 1 prior line of therapy in the retrospective review compared to study AG221-C-001 (70% vs. 46.2%), while the number of patients who had failed prior HSCT (19% and 13.6%, respectively) or with prior MDS (17% vs. 21.5%, respectively) was similar. A higher fraction of subjects in study AC221-C-001 had refractory disease compared to the retrospective review (39.3% vs. 24%). Subjects with poor risk cytogenetics were more common in the pivotal study compared to the retrospective review (25.7% vs. 8%, respectively). Median OS according to the primary analysis definition was 7.2 months (95%CI 4.7, 10.7), and 7.23 (95%CI 4.7, 10.7) in the sensitivity analysis starting from the proposed alternative

baseline. 5-azacytidine- or cytarabine-containing regimens were the most common treatments used in second and subsequent lines of therapy (31% and 32%, respectively), while 33% of subjects received intensive chemotherapy +/- gemtuzumab. ORR was 30% (95%CI 21%, 40%) and CR rate was 22.3% (21/94).

The AMLSG database includes AML patients for whom data were collected as part of an AMLSG study or clinical registry. Five studies were selected by AMLSG for inclusion in the AMLSG historical control analyses. The patients in these studies had a confirmed IDH2 mutation status at the time of the diagnosis and had not received enasidenib.

The primary analysis was chosen to be an optimal 1:1 matching approach based on the logit transform of the propensity scores (LTPS). To make analyses more robust, PS methods were applied in conjunction with multivariable regression adjustments for OS analyses using covariates identified by clinical experts for PS estimation.

After optimal 1:1 matching, sample size in each group was reduced to the number of patients in the smaller cohort. Overall survival is summarized for the primary analysis for Study AG221-C-001 and French Chart Review SoC, and for Study AG221-C-001 and AMLSG SoC in Table eff 25. The median OS was longer for the enasidenib group than for the French Chart Review SoC group (9.3 vs 4.8 months, respectively) and the AMLSG SoC (8.3 vs 5.5 months, respectively), as were the 3- and 12-month survival.

Table eff 25: Overall Survival Kaplan-Meier Matching 1:1 Analyses of Study AG221-C-001, French Chart Review, and AMLSG

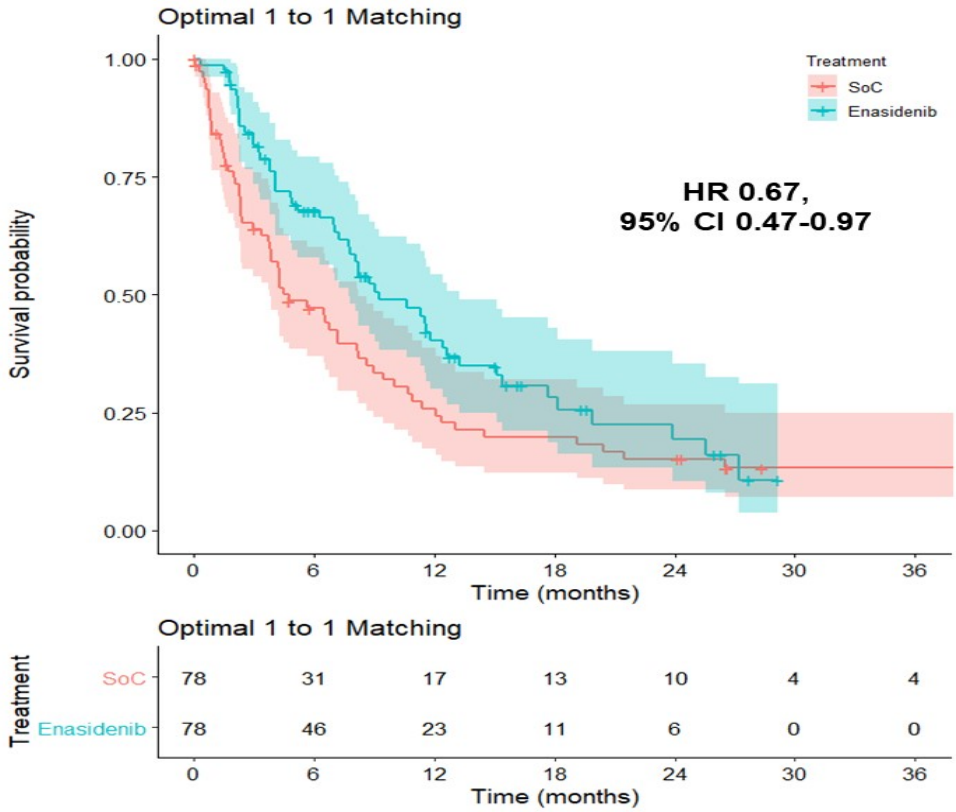
Parameter	French Chart Review		AMLSG Study	
	Primary Analysis		Primary Analysis	
	Enasidenib 100 mg	Standard of Care	Enasidenib 100 mg	Standard of Care
Sample Size	78	78	178	178
Number of deaths	52	63	135	147
Median OS (months)	9.3	4.8	8.3	5.5
95% CI	7.7, 13.2	3.8, 8.2	7.3, 9.5	4.3, 6.4
3-month survival rate (%)	82	64	78	63
95% CI	73, 91	54, 76	72, 84	56, 70
12-month survival rate (%)	40	26	32	29
95% CI	30, 54	17, 39	26, 41	23, 37

AMLSG = acute myeloid leukemia study group; CI = confidence interval; OS = overall survival.
Source: French Chart Review PSM Report Table 4 and AMLSG PSM Report Table 7

Kaplan-Meier (KM) OS curves are presented in Figure eff 8 for matching with the French Chart Review SoC and in Figure eff 9 for matching with AMLSG SoC. After adjusting for covariate risk factors, mortality risk was significantly lower in the enasidenib group than in both the SoC group from the French Chart Review (HR 0.67; 95% CI 0.47, 0.97) and the SoC group from AMLSG (HR 0.74; 95% CI 0.59, 0.93).

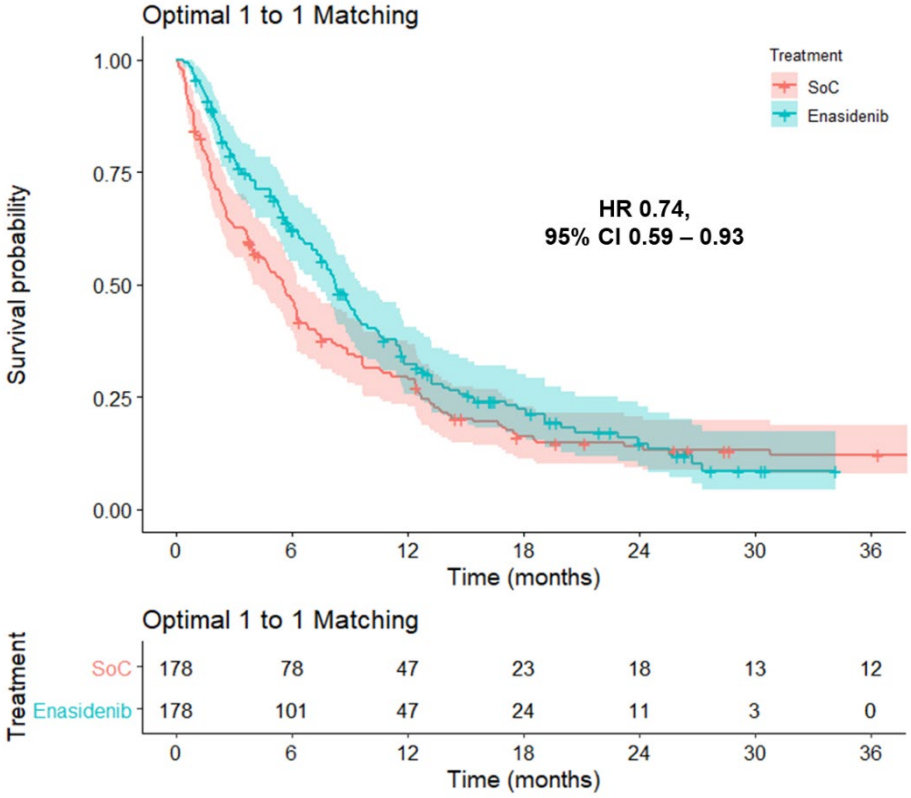
The tail ends of both KM curves should be interpreted with caution, considering the small number of remaining patients.

Figure eff 8: Kaplan-Meier Estimated OS, 1:1 Optimal Propensity-Matched Sample of Enasidenib (AG221-C-001) and SoC (French Chart Review Study)



CI = confidence interval; HR = hazard ratio; OS = overall survival; SoC = standard of care.
The reported HR and 95% CI (depicted by the shaded areas) were estimated from a Cox proportional hazards analysis of the matched sample using a robust variance estimator to account for the presence of matching.
Source: French Chart Review PSM Report Figure 4.

Figure eff 9: Kaplan-Meier Estimated OS, 1:1 Optimal Propensity-Matched Sample of Enasidenib (Study AG221-C-001) and Standard of Care (AMLSG Study)



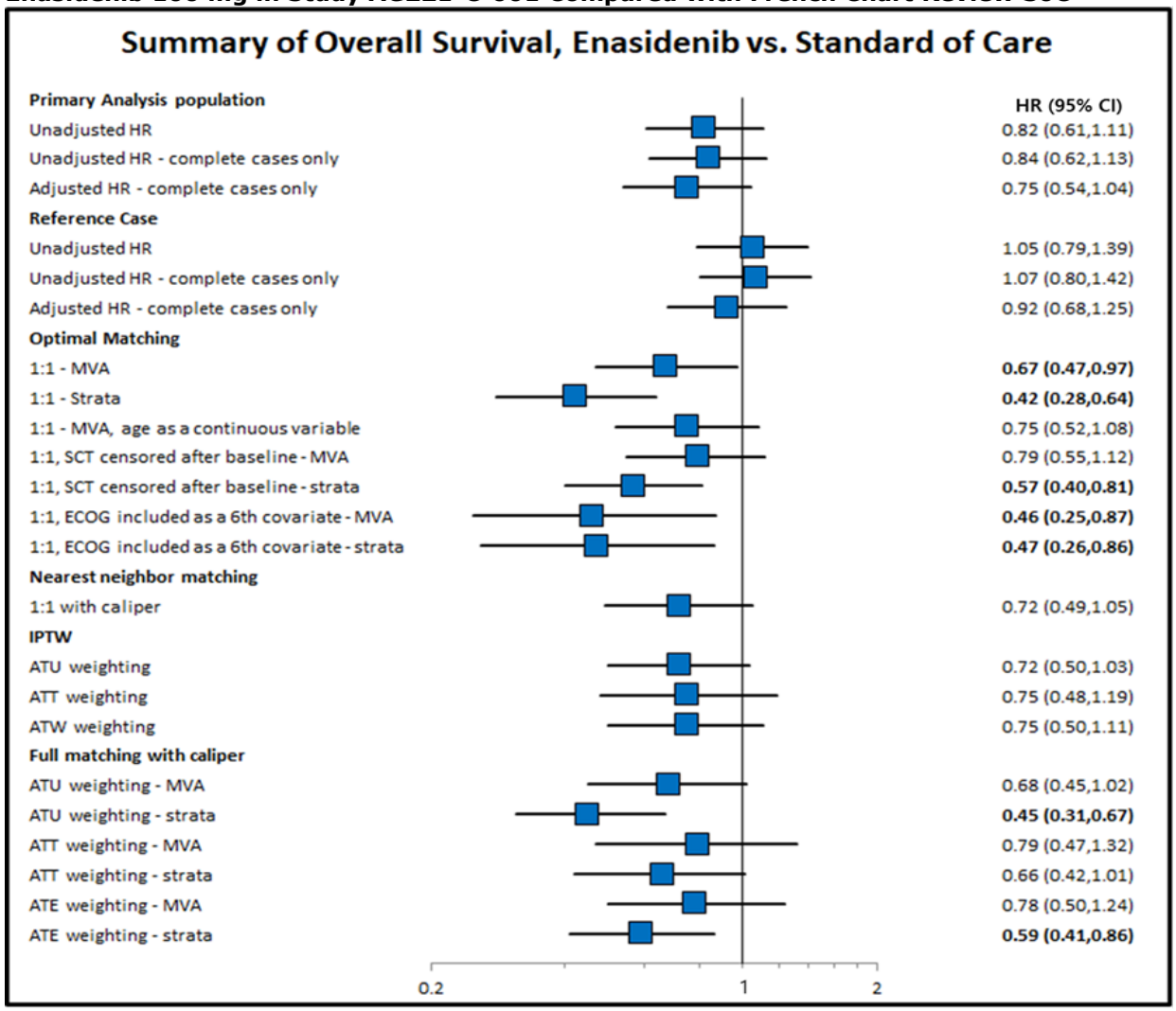
CI = confidence interval; HR = hazard ratio; OS = overall survival; SoC = standard of care.

The reported HR and 95% CI were estimated from a Cox proportional hazards analysis of the matched sample using a robust variance estimator to account for the presence of matching.
Source: AMLSG PSM Report Figure 3.

After matching and adjusting for covariate risk factors, mortality risk was significantly lower in the enasidenib group than in both the SoC group for the French Chart Review (HR 0.67; 95% CI 0.47, 0.97) and from AMLSG (HR 0.74; 95% CI 0.59, 0.93). For both the French Chart Review and AMLSG comparisons to Study AG221-C-001, the median OS was longer for enasidenib, as were the 3- and 12-month survival. For the AMLSG cohort, after matching and adjusting for the 5 covariate risk factors plus ECOG, mortality risk was significantly lower in the enasidenib group than in the SoC group from AMLSG (HR 0.70; 95% CI 0.55, 0.89).

To assess the robustness of these findings, a series of sensitivity analyses were performed using well-established matching and weighting methods. The primary analysis and sensitivity analyses are presented for Study AG221-C-001 compared with the French Chart Review SoC and AMLSG SoC in the Forest plots in Figure eff 10 and Figure eff 11.

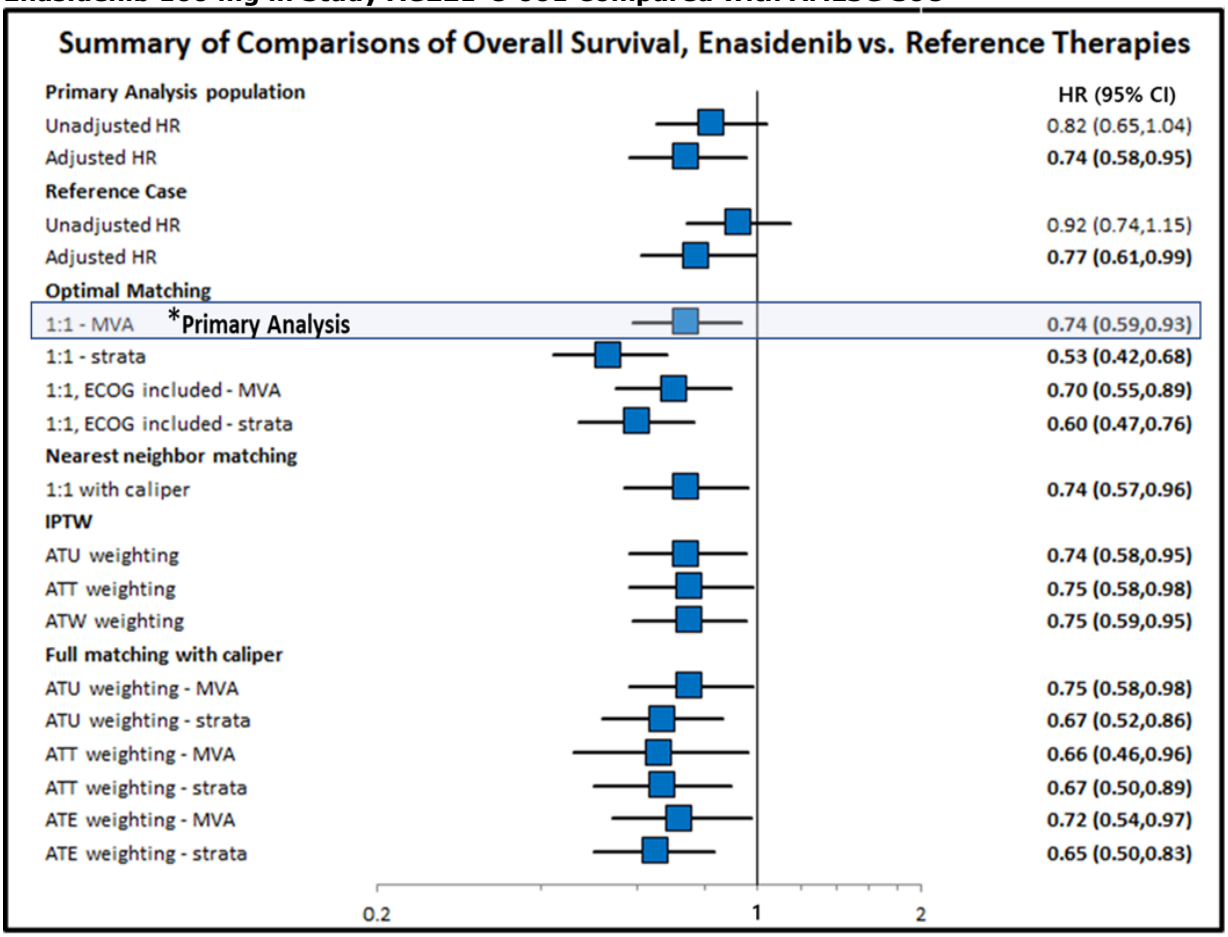
Figure eff 10: Forest Plot of Comparison of OS for the Primary and Sensitivity Analyses for Enasidenib 100 mg in Study AG221-C-001 Compared with French Chart Review SoC



ATE = average treatment effect in the entire population; AML = acute myeloid leukemia; ATT = average treatment effect in the treated; ATU = average treatment effect in the untreated population; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IPTW = inverse probability treatment weighting; MDS = myelodysplastic syndrome; MVA = multivariable adjusted; OS = overall survival; PSM = propensity score matching; SCT = stem cell transplantation; SoC = standard of care.
Note: Results denoted as 'MVA' indicate hazard ratios derived from Cox proportional hazards analyses that included multivariable adjustments for age, prior stem cell transplant, cytogenetic risk, history of MDS and number of prior lines of AML therapy. Results denoted as 'Strata' indicate hazard ratios derived from Cox proportional hazards analyses that included an adjustment for propensity score matched strata of treated and control patients.
Hazard ratios < 1 favor enasidenib 100 mg daily, and statistically significant differences are shown in bolded font.

"Primary Analysis Population" means pre-matched analysis done on the same population than for the "Primary Analysis" (ie, RAS, all patients excluding those with post-baseline HSCT). "Reference Case" means pre-matched FAS, all patients including those with post-baseline HSCT. Optimal 1:1 matching MVA is the primary analysis.
Source: French Chart Review PSM Figure 5.

Figure eff 11: Forest Plot of Comparison of OS for the Primary and Sensitivity Analyses for Enasidenib 100 mg in Study AG221-C-001 Compared with AMLSG SoC



ATE = average treatment effect in the entire population; AML = acute myeloid leukemia; AMLSG = acute myeloid leukemia study group; ATT = average treatment effect in the treated population; ATU = average treatment effect in the untreated population; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IPTW = inverse probability treatment weighting; MVA = multivariable adjusted; MDS = myelodysplastic syndrome; OS = overall survival; PSM = propensity score matching; SoC = standard of care.

Clinical studies in special populations

NA

Analysis performed across trials (pooled analyses AND meta-analysis)

NA

Supportive study(ies)

NA

3.3.6. Discussion on clinical efficacy

Basics

The efficacy claims of enasidenib in IDH2 mutant R/R AML patients are based on a single pivotal uncontrolled phase 1/2 study, namely study AG221-C-001.

To assess the benefit and value of enasidenib in the context of existing therapies used in the R/R AML population, the Applicant performed

- a systematic review of published literature and
- a comparison of the AG221-C-001 data versus AML registry data collected in R/R AML patients with an IDH2 mutation treated with conventional treatments in a real-world setting (the mentioned registries being the AMLSG (Germany) and PETHEMA (Spain)).
- A propensity score matching analysis of study AG221-C-001 vs French Chart Review and vs AMLSG

To further support these results in the proposed indication in the scope of a CMA application, the Applicant proposes confirmation of benefit-risk (overall survival) as a post-authorisation measure with submission of the clinical study report from the ongoing open-label randomised controlled phase 3 study AG-221-AML-004 (IDHENTIFY) comparing enasidenib monotherapy with conventional care regimens in an elderly (≥60 years) late stage (2nd and 3rd relapse) IDH2 mutated R/R AML population (primary endpoint: OS).

AML is agreed to be a life-threatening disease.

Enasidenib was designated an orphan medicinal product in the EU for the treatment of AML on 28 Apr 2016 (EU/3/16/1640). The application for orphan drug designation was based on the criterion of significant benefit over existing methods of treatment for the condition.

Frequency and clinical outcomes of IDH2 mutations in AML

The frequency of reported IDH2 mutations is between 8.2% and 19.3%, with a weighted average of 11.2%. In subjects with IDH2 mutated AML, the R140 mutation is the more common and represents approximately 70% of the cases, while the R172 mutation represents approximately 30%.

The prognostic impact of mutated IDH2 in AML remains controversial. As to Medeiros 2017, several studies have suggested an association with adverse outcomes whereas others have failed to identify any clear influence on clinical response or survival and still others report improved survival. Differences in prognostic findings may reflect variations in study methodologies; also the mutational context may influence AML prognosis. Currently it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH2 in AML and further confirmation in prospective studies is needed to more clearly elucidate the effect.

Design and conduct

Study AG221-C-001
Study AG221-C-001 is an uncontrolled, open-label, multicentre first-in-human phase 1/2 study.

Phase 1 is divided in a dose escalation and a dose expansion part. Subjects included in phase 1 were patients with advanced haematologic malignancies with an IDH2 mutation, i.e. the R/R AML population was just a subpopulation in phase 1. In phase 2 only patients with IDH2 mutated R/R AML were included.

Since initiation the study was amended 7 times, finally with the aim to use it as pivotal evidence in an MAA. Amendments of this study performed in an open-label design include modifications of the study population, posology of the study drug, schedule of assessments, statistical methodology, study

endpoints, sample size (list incomplete). In conclusion, data provided from study AG221-C-001 are exploratory, analyses performed are descriptive.

The study population included in study AG221-C-001 (especially in phase 2) is considered representative of a very high-risk R/R AML population with few effective alternatives [i.e. patients with curative options (i.e. intensive chemotherapy and/or HSCT) were excluded; in phase 2, patients in the first relapse were only included in case of relapse within 1 year of initial treatment or after HSCT; in phase 2, patients with favourable-risk status according to NCCN 2015 [i.e.: inv(16), +(16;16), t(8;21), t(15;17)] were excluded].

Furthermore, it is notable that the study population is very heterogeneous, which makes the comparison with external/historical controls complicated. Factors such as age at relapse, relapsed or refractory disease, nature of AML (de novo vs secondary), cytogenetics, relapse-free interval from first CR, number of prior therapies, prior HSCT, the performance status of the patients (list incomplete) all affect to different degrees response to treatment and survival.

Efficacy endpoints as defined in the study protocol are adequate for a phase 1/2 trial and in this early trial setting they sufficiently reflect the study objectives. However, regarding the registrational claim of the study fundamental limitations are noted:

- EFS, CR rate and CR/CRi/CRp rate are not considered established or validated surrogate markers for OS in AML.
- No hierarchy of the efficacy endpoints is predefined in the study protocol. A hierarchy can only be found in the SAP with ORR as primary endpoint. This hierarchy is further weakened by the fact that no hypotheses tests were pre-specified, AG221-C-001 being an uncontrolled phase 1/2 trial without confirmatory claim.
- ORR in study AG221-C-001 is defined as the rate of responses (CR, CRi, CRp, PR, MLFS). This definition of ORR is broader than the one typically used in AML, which would only include CR+CRi/CRp. This is understood due to the fact that the original intent of the phase 1/2 study was to identify an efficacy signal with enasidenib. However, the clinical relevance of ORR is unclear in the AML setting. In conclusion, ORR is not acceptable as the main efficacy endpoint for registrational purposes.
- Analyses to support the clinical benefit, such as, e.g., transfusion independence, rates of infection, bleeding, and neutropenia during response periods are certainly clinically relevant, but results are considered difficult to interpret because of the potential for bias and the lack of a control making it impossible to establish the size of effect attributable to treatment in the frame of an uncontrolled trial. In addition, transfusion history was only partially collected prospectively and of note, the endpoints regarding transfusion independence were added retrospectively in the knowledge of the results.
- Contribution of treatment to time related endpoints such as OS and EFS cannot be directly ascertained in a single arm study.

In conclusion, efficacy assessment of the uncontrolled phase 1/2 study AG221-C-001 presented as single pivotal evidence will primarily focus on CR rate and Duration of CR. OS is seen as the relevant endpoint for contextualisation of the results of study AG221-C-001 (i.e. the comparison with external/ historical controls).

The sample size for Phase 1 was mainly justified based on safety considerations (maximal width of the 95% CI for toxicity rates at the MTD, probability to observe AEs).

For the phase 2 part, it is not fully clear whether the sample size was determined in dependency of the CR rate and ORR that can be considered as minimal clinically significant activity, or vice versa (i.e. whether a sample size was chosen and a justification was sought why the lower bound of the 95% CI that was considered achievable represents minimal clinically significant activity).

The statistical analyses were appropriate for a phase 1/2 study.

External controls

Literature review
A systematic review of the literature was performed to identify large published studies in R/R AML, regardless of IDH2 mutation, that included conventional treatment options which may be used to compare against the AG221-C-001 data. Furthermore, the literature review included the search for IDH2 mutation positive AML, irrespective of the line of therapy.

In the course of the MAA the Applicant presented a further literature review trying to identify studies in the R/R AML setting with azacitidine (Vidaza®) or cytarabine, as both products have partially overlapping indications with the proposed indication for enasidenib. Six studies were identified, two phase 3 studies using high-dose cytarabine (HiDAC) (Faderl et al 2012; Ravandi et al 2015), one retrospective study with low-dose cytarabine (LDAC) (Sarkozy et al 2013), one uncontrolled phase 1/2 study with azacitidine (Al-Ali et al 2012) and two retrospective studies with azacitidine (Ivanoff et al 2013, Itzykson et al 2015).

Comparison to registry data based on matching adjusted indirect comparison (AMLSG + PETHEMA)
In order to understand the OS benefit of enasidenib in the context of conventional therapies available for patients in the R/R AML setting, the AG221-C-001 data have been compared retrospectively to a subset of patients from both the AML Study Group (AMLSG) Bio registry and the Programa Espanol de Tratamientos en Hemtologia group (PETHEMA) registry. Of note, registry data presented are aggregated data; individual patient data are not available. Matching-adjusted indirect comparison was applied by assigning weights to the patients from AG221-C-001 such that summary statistics for three key prognostic factors in the weighted population are the same as in the population from the patient registry to be compared with.

Propensity score matching (AMLSG + French chart review)
The applicant's third approach was to put OS observed in Study AG221-C-001 into the context of the therapeutic landscape by comparing the results with real-world efficacy data collected in a comparable population (according to the inclusion criteria of Study AG221-C-001) from a similar group of patients treated with SoC from the French Chart Review Study and a similar group of patients treated with SoC from the AMLSG Bio Registry. Propensity score matching for 5 matching covariates was performed to reduce differences in these prognostic factors.

Efficacy data and additional analyses

Study AG221-C-001
Study AG221-C-001 started recruitment in September 2013 and the study is still ongoing (recruitment: complete; treatment ongoing: n=16; study ongoing: n=54). Overall 345 patients with IDH2 mutated advanced haematologic malignancy were included into that trial, 280/345 had R/R AML in diverse posologies. The efficacy data presented for study AG221-C-001 in this current MAA are focussing only on the data from the subpopulation of 214 R/R AML subjects treated with enasidenib monotherapy 100 mg daily based on a data cut-off date of 01 Sep 2017.

As to the key baseline demographics and disease characteristics the R/R AML study (sub)population receiving enasidenib monotherapy 100 mg daily represents an advanced IDH2 mutated R/R AML

population (median age: 68 years; relapsed disease: 60.7%; intermediate risk cytogenetics: 50.5%; prior MDS: 11.5%; AML not otherwise specified according to WHO classification: 53.7%; median number of prior anticancer therapies: 2.0; prior regimens 1/2: 47.2% and 30.4% respectively; R140 IDH2 mutation: 75.7%). However, some issues remain to be clarified.

A total of 42/214 (19.6%; 95% CI 14.5, 25.6) subjects in the combined Phase 1/2 R/R AML population treated with 100 mg enasidenib daily achieved a best response of CR (investigator assessment). Duration of CR was 7.4 months (95% CI 6.5, 16.3) for the combined phase 1/2 population. 'CR+CRi+CRp' rate and ORR and their respective duration of response and the presented sensitivity analyses are regarded as supportive of the discussed CR data. In conclusion, this data suggest promising clinical activity of enasidenib monotherapy in the studied population. However, the shown effect size is certainly not sufficiently outstanding to justify conditional approval without contextualisation of this effect.

Best response in patients is regularly achieved not before cycles 5-7 indicating that treatment with enasidenib should be continued until cycles 5-7 unless experiencing disease progression or unacceptable toxicities.

Median OS in the R/R AML population treated with enasidenib 100 mg daily was 8.8 months (95% CI 7.7, 9.6). Median OS was longer for patients achieving CR compared to patients achieving 'CR+Cri/CRp' and non-responders. However, the analysis of OS according to response status is influenced by immortal time bias (i.e. patients need to have survived for some time in order to achieve response) such that a clear conclusion on the causal relationship between response and longer survival time is not possible based on these data. The OS effect is certainly of interest and supports the CR results discussed above. However, contribution of treatment to time related endpoints such as OS cannot be directly ascertained in an uncontrolled study and therefore needs contextualisation especially having in mind the very heterogeneous study and target population. Furthermore, it needs to be discussed whether informative censoring occurred and had an influence on the OS results.

A total of 19/214 (8.9%) R/R AML patients were able to electively discontinue enasidenib and to directly proceed to allogeneic HSCT. Most of the 19 subjects achieved a CR or CRi/CRp (n=14; 73.9%). Median OS from the first dose date of enasidenib was 23.6 months (95% CI: 10.6, NA) and by this was in the same range than for the CR overall R/R AML population receiving enasidenib monotherapy until progression or unacceptable toxicity [22.9 months (95% CI: 13.2, NE); n= 42]. This supports the feasibility of allo-HSCT after treatment with enasidenib in the R/R AML setting in selected subjects. However, as numbers are very low in an uncontrolled setting and only sparse efficacy/safety data were collectecd in the post-HSCT setting, further randomised controlled studies will be necessary, to clarify, whether R/R AML patients show a clinically relevant benefit from allo-HSCT after adequate response under enasidenib monotherapy.

Data regarding transfusion (in)dependence show that treatment with enasidenib can reduce transfusion dependence or maintain transfusion independence both for RBC and platelets. This reduction in transfusion dependence or maintenance of transfusion independence was not restricted to subjects who achieved CR, but was consistent in non-CR responses. However, although transfusion independence in principle could be a clinically relevant endpoint, it cannot be accepted as a pivotal endpoint for regulatory decision-making for the following reasons:

- The endpoints regarding transfusion independence were added retrospectively in the knowledge of the results
- The Applicant's definition of transfusion (in)dependence ("at least 1 RBC within 8 week period at baseline") is not considered robust. It is referred to the definition applied by the same applicant for lenalidomide in the treatment of MDS, which reads "*RBC-transfusion-dependent anaemia defined as receiving ≥ 2 units of RBCs within 8 weeks of the first day of study treatment. Patients must have received at least 2 transfusions in each of the 8-week periods during the 16-week*

pre-treatment period and must not have been transfusion free for any 56 consecutive days during the 16-week pre-treatment period."

- As no universally agreed definition of transfusion (in)dependence exists, it is notable, that the definition of this endpoint was performed in the knowledge of the study data.
- Transfusions were administered according to clinical evaluation, which could vary according to country and institution policy.
- Transfusion history was only partially collected prospectively

In consequence, no relevant efficacy claims regarding benefit/risk assessment in an MAA can be derived from this descriptive data.

Subjects who achieved a response had reduced incidence of grade 3/4 infection and bleeding, and febrile neutropenia during the periods of response compared with non-responders. However, this finding is not surprising as haematologic improvements in platelets, haemoglobin and ANC, such as those associated with response to enasidenib or other AML therapeutics, are generally accompanied by a reduction in adverse events associated with these laboratory parameters; i.e. bleeding events, infections and febrile neutropenia. Furthermore, the magnitude of the effect cannot be contextualised due to the uncontrolled study design and effect size is not outstanding. The comparison to historical control is not deemed acceptable also for this endpoint, as too many confounding factors impact infections and bleeding. In consequence, no relevant efficacy claims regarding benefit/risk assessment in an MAA can be derived from this descriptive data.

External controls

Literature review

With respect to the published data available from the literature it is obvious that the high heterogeneity in populations had clearly a significant impact on the outcome. As the population differs significantly it remains critical to perform any valid comparison regarding efficacy. Moreover, in the listed trials the OS-Origin dates vary between the trials (Date of initial diagnosis/ Date of randomisation/ Date of treatment start etc.). This is also reflected in the wide range of the reported median OS between 3.3 months in the advanced stage population of Roboz and up to 13.1 months in the first relapse population described by Paschka. Efficacy comparison is hindered by the limited data available and there is a lack of controlled data for azacitidine and partially the studies were performed as retrospective analyses. Thus, from a regulator's perspective, it remains impossible to confirm a clear benefit regarding OS for the product applied for from the provided comparison with literature data.

Comparison to registry data based on matching adjusted indirect comparison (AMLSG + PETHEMA)

From a regulatory point of view, also the confirmative value of the registry data is overall low and again not acceptable for a reliable comparison. Regarding the PETHEMA cohort, there is a general concern that the results from a comparison to this small sized cohort do not allow reliable conclusions, which is supported by the wide confidence intervals for the median survival and 3- and 12-months survival.

With respect to the details of the general approach used for analysis of the registry data the following issues need to be considered: It is well known that indirect comparisons are susceptible to bias due to confounding. The distribution of key prognostic factors was different in the study population of AG221-C-001 and in the patient registries. The attempt of the applicant to provide a more reliable comparison by standardization for known confounders is acknowledged. However, individual patient data were not available from the patient registries but only aggregated data. Therefore, matching-adjusted indirect comparison was applied by assigning weights to the patients from AG221-C-001 such that summary

statistics for three key prognostic factors in the weighted population are the same as in the population from the patient registry to be compared with.

However, the fact that summary statistics are equal does not imply that distributions are equal (or similar) such that there may still be differences between the treatment groups with regard to the prognostic factors accounted for in spite of standardization (only for categorical variables, distributions are truly equal if summary statistics are equal, but categorization of continuous variables such as age leads to a loss of information).

Furthermore, there are general concerns on the robustness of the matching-adjusted indirect comparison. Weighting could lead to a situation where the outcomes in a subset of patients with large weights have a major influence on the results while patients with small weights are almost disregarded such that the results may mainly be based on outcomes in a substantially smaller population than the original population. Patients with large (small) weights may especially occur when there are large baseline imbalances which have to be corrected for by major differences in the weights of the patients. In particular, as no details on the calculation of 95% confidence intervals for median and 3- and 12-month survival were given, these were probably calculated using standard methods assuming that the weights are fixed. However, weights were not fixed but selected in dependency of the test population. Ignoring the uncertainty due to the weight selection procedure leads to confidence intervals that are too narrow.

Generally, there is a concern that patients with a very poor health status after an R/R event may be unlikely to be included in a clinical trial while no such restriction exists for inclusion in a real-world data cohort. It is agreed that defining the date of relapse as baseline for the reference cohorts can be considered as conservative. However, the early separation of the curves implies that deaths in the R/R group were observed almost immediately after the R/R event while deaths in the clinical trial were observed only with some delay that is unlikely explained by treatment, supporting the concern on a differential selection of study population and control cohorts. This concern is even stronger because a substantial part of the difference in survival is explained by the early separation.

In conclusion, the approach for comparison proposed and particularly the indirect adjustment included does not allow adequate quantification of a potential survival benefit of enasidenib vs. historical controls.

Propensity score matching (AMLSG + French chart review)

The attempt of the applicant to provide context for the observed OS in study AG221-C-001 is acknowledged. Although propensity score matching accompanied by adjustment for covariates is in principle an appropriate method for indirect comparisons, the general limitations of indirect comparisons and some specific issues regarding the performed analyses need to be taken into account:

- Although reducing differences between treatment group and respective external control group with regard to the 5 matching covariates, the propensity score matching cannot establish comparability of the treatment group and the external control group. These 5 covariates, which were selected among a set of 15 covariates, represent only a small subset from the known prognostic factors potentially influencing OS in R/R AML (e.g. both Heinicke T et al. Blood 2014 and Ferrara F et al Haematologica. 2004 highlighted how response duration with prior treatments plays a relevant role in predicting survival in r/r AML). In addition, imbalances may exist with regard to yet unknown important covariates. Therefore, a conclusion that the observed differences in OS are causally explained by treatment is not valid because relevant confounding cannot be excluded and is even very likely. Additional propensity score analyses could match for a maximum of 7 covariates, which does not solve the fundamental underlying problem and was possible only at the cost of restriction of the comparison to a subgroup of the study population that is not necessarily representative for the broader population that is claimed in the indication.

- The concern for a relevant selection bias is supported by the fact that differentiation between the survival curves for the matched cohorts starts from the beginning of follow-up. This is inconsistent with the applicant's statement in the summary of clinical efficacy that – consistent with the mechanism of action of enasidenib and quite different from classic cytotoxic compounds used in this setting – response to enasidenib takes time (Applicant's Clinical Overview, section 4.1.4.2.1.: "In the 42 subjects who achieved a best response of CR, 19.0% achieved CR by Cycle 3, 59.5% by Cycle 5, and 83.3% by Cycle 7, indicating that subjects should be treated for at least 6 cycles unless experiencing disease progression or unacceptable toxicities."). The early differentiation explains a substantial proportion of the observed differences between the matched cohorts. Even if landmark analyses show that differences are not only explained by patients who died within the first month, the underlying concern that baseline differences not explained by known covariates exist is not resolved because it is unlikely that the possible unexplained baseline differences are completely explained by patients who died within 1 month.

In conclusion, as acknowledged by the applicant, indirect comparisons through PSM are subject to multiple sources of bias such that the comparisons to external controls are not considered adequate to demonstrate efficacy. The comparison of OS to external controls based on propensity score matching is considered as relevant supportive information but cannot establish evidence for benefit of treatment in itself.

3.3.7. Conclusions on clinical efficacy

Efficacy of enasidenib is claimed from results of Study AG221-C-001, which is an uncontrolled, open-label, multicentre first-in-human phase 1/2 study which means that data provided are limited and analyses performed are exploratory.

The relevance of the observed CR effect size is certainly not sufficiently outstanding to justify conditional approval without contextualisation of this effect and median OS in the R/R AML population of 8.8 months (95% CI 7.7, 9.6) is currently unclear. The presented data from external controls [published literature, registries (vs AMLS and vs PETHEMA) and propensity score matching (vs French chart review and vs AMLSG)] is deemed not sufficient to allow a valid comparison regarding efficacy with the OS outcome of AG221-C-001.

3.3.8. Clinical safety

The primary focus of the safety analyses for this submission is on *Study AG221-C-001* in subjects with advanced hematologic malignancies with an IDH2 mutation.

The combined AG221-C-001 Phase 1/2 study included a total of 345 enrolled subjects, of whom 280 were subjects with R/R AML with an IDH2 mutation. Of these 280 subjects, 214 were assigned to enasidenib 100 mg daily dose treatment. Sixteen subjects remained on treatment as of the cut-off date. However, the safety data is presented as a combined Phase 1 /2 analyses. The median duration of exposure to enasidenib was 4.2 months; the mean duration of exposure was 6.5 months respectively.

Because Study AG221-C-001 was a single-arm study without an active comparator arm, additionally a systematic literature review was performed to identify published studies in subjects with R/R AML to which the safety data from this study could be compared. Three studies were selected: a Phase 1/2 study of gilteritinib, and two Phase 3 studies, CLASSIC I and VALOR, which both included a cytarabine plus placebo treatment arm. For all three comparisons, due to a longer duration of exposure in Study

AG221-C-001, only TEAEs with onset during the first three cycles of enasidenib treatment were included in the evaluations.

Additional safety data came from sponsored ongoing studies in subjects with hematologic malignancies (AG-221-AML-004, AG-221-AML-005, AG120-221-C-001), an Investigator initiated trial (BAML-16-001-S3), completed studies in healthy subjects (AG221-C-002, AG-221-CP-001, and AG-221-CP-002) and one completed study in subjects with solid tumours (AG221-C-003). Overall, 688 adults were exposed to enasidenib (healthy subjects: n=106; any AML: n=535; R/R AML: n=396; MDS and others malignancies: n=47). Further safety information regarding the use of enasidenib outside from clinical trials came from the compassionate use program and post-marketing reports in the US.

Safety assessments included adverse events (AEs) and deaths, clinical laboratory information, vital sign measurements, 12-lead electrocardiograms (ECGs), and left ventricular ejection fraction (LVEF). Details concerning safety assessments and data collection times are available in the individual study protocols.

Additional safety assessments were done by organ system or syndrome and included evaluation of enasidenib related (IDH) differentiation syndrome, non-infectious leukocytosis, tumor lysis syndrome, gastrointestinal disorders, hyperbilirubinemia and hepatic safety, renal safety, cardiac safety, blood and lymphatic system disorders, and infections. The additional safety assessments included evaluations of grouped TEAEs, laboratory parameters, and ECGs. Analyses were presented for the subjects in the combined Phase 1/2 population of Study AG221-C-001 unless otherwise noted.

Demographics and baseline characteristics

Across the Safety Analysis Set of 345 patients from study AG221-C-001, the majority were male (58.3%) and white (77.4%). The median age was of 69 years and the majority of patients (67%) were aged 65 years or older. ECOG Performance status (PS) was of ≥ 1 in 265 patients (76.8%). In 65 patients, data about UGT1A1 mutations were available (43 of these mutated, 27 heterozygous and 16 homozygous). The majority of patients were diagnosed as R/R AML (81.2%). Overall, 264 patients (76.5%) had a normal value of creatinine clearance, 54 (15.7%) values between 45 and 60 mL/min and the remaining 26 (7.5%) under 45 mL/min. Similar demographic features were observed in the other ongoing studies, expect for a lower median age in AG120-221-C-001 and in AG221-C-003 studies (61 and 62 years, respectively).

Patient exposure

The dosage of enasidenib was established on the basis of phase 1 dose-escalation, a phase 1 expansion part and a phase 2 study and finally fixed to 100 mg QD on days 1 to 28 in 28-days cycles. The drug was administered until progression and/or unacceptable toxicity. In combined phase 1/2 AG221-C-001 study (Safety Analysis Set) the median duration of Enasidenib administration was of 4.2 months (0.1-34.1), with a median number of cycles of 7.3 (1.0-38.0). The median time of treatment duration and duration of treatment exposure was of 4.6 months (0.3-34.1) and 5.4 months (0.4-34.2) for patients with R/R AML treated with 100 mg of Enasidenib. One-hundred and eighty-three patients (53%) received 5 or more cycles of Enasidenib treatment and only 55 (15.9%) more than 12 cycles.

As presented in table OVsaf01, at data cut off 95.4% of all patients discontinued treatment, mainly due to disease progression. 84.3% of patients discontinued the study.

Table OVsaf01: Subject disposition by malignancy types and overall, combined Phase1/2

	R/R AML (N=280) n (%)	Untreated AML (N=39) n (%)	MDS (N=17) n (%)	Others (N=9) n (%)	Overall (N=345) n (%)
Treatment Status					
Ongoing	11 (3.9)	3 (7.7)	0 (0.0)	2 (22.2)	16 (4.6)
Discontinued	269 (96.1)	36 (92.3)	17 (100.0)	7 (77.8)	329 (95.4)
Treatment Discontinuation	269 (100.0)	36 (100.0)	17 (100.0)	7 (100.0)	329 (100.0)
Withdrawal of consent	15 (5.6)	4 (11.1)	0 (0.0)	0 (0.0)	19 (5.8)
Due to Adverse Event or DLT	34 (12.6)	4 (11.1)	3 (17.6)	2 (28.6)	43 (13.1)
Any medical condition which, in the opinion of the Investigators, would put the subject at risk for continuing treatment	4 (1.5)	0 (0.0)	1 (5.9)	0 (0.0)	5 (1.5)
Experiences disease progression	133 (49.4)	13 (36.1)	5 (29.4)	2 (28.6)	153 (46.5)
Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial	3 (1.1)	0 (0.0)	0 (0.0)	1 (14.3)	4 (1.2)
The Investigator removes the subject from the trial in the best interests of the subject	7 (2.6)	3 (8.3)	1 (5.9)	0 (0.0)	11 (3.3)
Subject requires use of a prohibited concomitant medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation: non-adherence to study drug regimen or protocol requirements	0 (0.0)	2 (5.6)	0 (0.0)	0 (0.0)	2 (0.6)
Lost to follow-up	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	31 (11.5)	5 (13.9)	2 (11.8)	1 (14.3)	39 (11.9)
Bone Marrow Transplant	26 (9.7)	2 (5.6)	2 (11.8)	1 (14.3)	31 (9.4)
Other	15 (5.6)	3 (8.3)	3 (17.6)	0 (0.0)	21 (6.4)
Study Status					
Ongoing	39 (13.9)	8 (20.5)	3 (17.6)	4 (44.4)	54 (15.7)
Discontinued	241 (86.1)	31 (79.5)	14 (82.4)	5 (55.6)	291 (84.3)
Study Discontinuation	241 (100.0)	31 (100.0)	14 (100.0)	5 (100.0)	291 (100.0)
Withdrawal of consent	22 (9.1)	4 (12.9)	1 (7.1)	0 (0.0)	27 (9.3)
Lost to follow-up	7 (2.9)	1 (3.2)	0 (0.0)	1 (20.0)	9 (3.1)
Death	182 (75.5)	21 (67.7)	10 (71.4)	3 (60.0)	216 (74.2)
Other	30 (12.4)	5 (16.1)	3 (21.4)	1 (20.0)	39 (13.4)

Adverse events

Adverse events (AEs) and Treatment-emergent adverse events TEAEs in study AG221-C-001 were defined and coded using MedDRA version 20.0.

TEAE were defined as AEs occurring between the start of Enasidenib and 30 days after the end of the last administration during the study. AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.03.

The severity (or intensity) of AEs will be assessed according to the CTCAE, version 4.0, May 28, 2009 (v4.03: June 14, 2010).

If an AE term is not listed in the CTCAE classification, the severity of the event will be assessed as follows:

- **Grade 1 – Mild Adverse Event:** Asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated.
- **Grade 2 – Moderate Adverse Event:** Minimal local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily life.
- **Grade 3 - Severe Adverse Event:** Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily life;
- **Grade 4 - Life-threatening or disabling Adverse Event:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 - Death:** Death related to the AE.

Table OVsaf02 presents a summary of all treatment-emergent adverse events for all patients with R/R AML by total daily dose of 100mg and overall.

Table OVsaf02: Summary of Treatment-emergent Adverse Events for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

TEAE Categories	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
TEAE	213 (99.5)	279 (99.6)	344 (99.7)
Related TEAE	178 (83.2)	227 (81.1)	284 (82.3)
Grade 3-4 TEAE	190 (88.8)	254 (90.7)	307 (89.0)
Related Grade 3-4 TEAE	91 (42.5)	124 (44.3)	151 (43.8)
Grade 5 TEAE	45 (21.0)	63 (22.5)	83 (24.1)
Related Grade 5 TEAE	1 (0.5)	1 (0.4)	2 (0.6)
TESAE	172 (80.4)	229 (81.8)	277 (80.3)
Related TESAE	61 (28.5)	78 (27.9)	92 (26.7)
TEAE leading to Discontinuation of Study Drug	36 (16.8)	49 (17.5)	65 (18.8)
Related TEAE leading to Discontinuation of Study Drug	9 (4.2)	13 (4.6)	16 (4.6)
TEAE Leading to Study Drug Dose Modification or Reduction	12 (5.6)	25 (8.9)	32 (9.3)
TEAE Leading to Study Drug Dose Interruption	96 (44.9)	129 (46.1)	162 (47.0)

AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, R/R AML = relapsed or refractory acute myeloid leukemia, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.
Data represent number (%) of subjects with at least 1 event. TEAEs were defined as any AEs that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related to study drug. CTCAE Grade version 4.03.
Data as of the 01 Sep 2017 cutoff.
Source: Table 14.3.1.1.7 of AG221-C-001and Table 14.3.1.1.9 of AG221-C-001.

Treatment-related treatment emergent adverse events

Table OVsaf3 summarizes the number of subjects with TEAEs suspected by the investigator of being treatment-related and that occurred in ≥ 3% of subjects overall.

Table OVsaf04 summarizes the number of subjects with suspected treatment-related TEAEs by maximum grade 3-4 that occurred in ≥ 1% of subjects overall.

Table OVsaf03: Treatment-related Treatment-emergent Adverse Events Reported in ≥ 3% of Subjects Overall by System Organ Class, Preferred Term for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

System Organ Class / Preferred Term	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
Subject With at Least 1 TEAE Reported as Treatment-related	178 (83.2)	227 (81.1)	284 (82.3)
Blood and Lymphatic System Disorders	**47 (22.0)**	**57 (20.4)**	**70 (20.3)**
Anaemia	14 (6.5)	18 (6.4)	25 (7.2)
Leukocytosis	16 (7.5)	22 (7.9)	25 (7.2)
Thrombocytopenia	7 (3.3)	11 (3.9)	15 (4.3)
Gastrointestinal Disorders	**96 (44.9)**	**121 (43.2)**	**151 (43.8)**
Constipation	7 (3.3)	10 (3.6)	12 (3.5)
Diarrhoea	33 (15.4)	45 (16.1)	52 (15.1)
Nausea	59 (27.6)	76 (27.1)	95 (27.5)
Vomiting	37 (17.3)	46 (16.4)	52 (15.1)
General Disorders and Administration Site Conditions	**57 (26.6)**	**73 (26.1)**	**90 (26.1)**
Asthenia	10 (4.7)	14 (5.0)	16 (4.6)
Fatigue	31 (14.5)	41 (14.6)	51 (14.8)
Oedema Peripheral	9 (4.2)	13 (4.6)	17 (4.9)
Pyrexia	13 (6.1)	14 (5.0)	15 (4.3)
Hepatobiliary Disorders	**22 (10.3)**	**29 (10.4)**	**33 (9.6)**
Hyperbilirubinaemia	16 (7.5)	21 (7.5)	24 (7.0)
Investigations	**95 (44.4)**	**127 (45.4)**	**157 (45.5)**
Alanine Aminotransferase Increased	15 (7.0)	18 (6.4)	21 (6.1)
Aspartate Aminotransferase Increased	20 (9.3)	24 (8.6)	29 (8.4)
Blood Alkaline Phosphatase Increased	6 (2.8)	10 (3.6)	14 (4.1)

Table OVsaf03: Treatment-related Treatment-emergent Adverse Events Reported in ≥ 3% of Subjects Overall by System Organ Class, Preferred Term for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)(continued).

System Organ Class / Preferred Term	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
Blood Bilirubin Increased	57 (26.6)	81 (28.9)	102 (29.6)
Electrocardiogram QT Prolonged	7 (3.3)	9 (3.2)	13 (3.8)
Platelet Count Decreased	6 (2.8)	9 (3.2)	13 (3.8)
Weight Decreased	11 (5.1)	15 (5.4)	16 (4.6)
Metabolism and Nutrition Disorders	**64 (29.9)**	**81 (28.9)**	**102 (29.6)**
Decreased Appetite	41 (19.2)	50 (17.9)	61 (17.7)
Hyperuricaemia	12 (5.6)	14 (5.0)	18 (5.2)
Tumour Lysis Syndrome	5 (2.3)	7 (2.5)	13 (3.8)
Nervous System Disorders	**41 (19.2)**	**53 (18.9)**	**70 (20.3)**
Dysgeusia	22 (10.3)	26 (9.3)	34 (9.9)
Headache	7 (3.3)	8 (2.9)	11 (3.2)
Peripheral Sensory Neuropathy	12 (5.6)	14 (5.0)	14 (4.1)
Respiratory, Thoracic and Mediastinal Disorders	**50 (23.4)**	**60 (21.4)**	**74 (21.4)**
Dyspnoea	20 (9.3)	21 (7.5)	27 (7.8)
IDH Differentiation Syndrome [a]	27 (12.6)	33 (11.8)	38 (11.0)
Skin and Subcutaneous Tissue Disorders	**45 (21.0)**	**57 (20.4)**	**69 (20.0)**
Pruritus	8 (3.7)	10 (3.6)	14 (4.1)
Rash	13 (6.1)	14 (5.0)	20 (5.8)
Rash Maculo-Papular	12 (5.6)	14 (5.0)	17 (4.9)

AE = adverse event, IDH = isocitrate dehydrogenase, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, R/R AML = relapsed or refractory acute myeloid leukemia, SOC = system organ class, TEAE = treatment-emergent adverse event.

Data represent number (%) of subjects. SOC and PT were coded using the MedDRA dictionary version 20.0. SOC and PT are sorted by alphabetic order. If a subject experienced multiple AEs under the same PT (SOC), then the subject was counted only once for that PT. TEAEs were defined as any AEs that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related.

[a] IDH differentiation syndrome was coded as the preferred term acute promyelocytic leukaemia differentiation syndrome.

Data as of the 01 Sep 2017 cutoff.

Source: Table 14.3.1.5.7 of AG221-C-001 and Table 14.3.1.5.9 of AG221-C-001.

Table OVsaf04: Treatment-related Treatment-emergent Adverse Events with Grade 3 or 4 Reported in > 1% Subjects Overall by System Organ Class, Preferred Term for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

System Organ Class / Preferred Term	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
Subject With at Least 1 Grade 3 or 4 Treatment-related TEAE	91 (42.5)	124 (44.3)	151 (43.8)
Blood and Lymphatic System Disorders	**27 (12.6)**	**34 (12.1)**	**43 (12.5)**
Anaemia	12 (5.6)	14 (5.0)	19 (5.5)
Febrile Neutropenia	8 (3.7)	8 (2.9)	8 (2.3)
Leukocytosis	4 (1.9)	7 (2.5)	8 (2.3)
Thrombocytopenia	7 (3.3)	10 (3.6)	13 (3.8)
Gastrointestinal Disorders	**10 (4.7)**	**14 (5.0)**	**15 (4.3)**
Nausea	5 (2.3)	8 (2.9)	8 (2.3)
General Disorders and Administration Site Conditions	**5 (2.3)**	**10 (3.6)**	**12 (3.5)**
Fatigue	2 (0.9)	5 (1.8)	6 (1.7)
Hepatobiliary Disorders	**6 (2.8)**	**10 (3.6)**	**11 (3.2)**
Hyperbilirubinaemia	4 (1.9)	7 (2.5)	8 (2.3)
Investigations	**28 (13.1)**	**46 (16.4)**	**60 (17.4)**
Alanine Aminotransferase Increased	4 (1.9)	4 (1.4)	5 (1.4)
Blood Bilirubin Increased	11 (5.1)	22 (7.9)	30 (8.7)
Lipase Increased	2 (0.9)	4 (1.4)	6 (1.7)
Neutrophil Count Decreased	3 (1.4)	3 (1.1)	4 (1.2)
Platelet Count Decreased	5 (2.3)	8 (2.9)	11 (3.2)
White Blood Cell Count Decreased	2 (0.9)	3 (1.1)	4 (1.2)
Metabolism and Nutrition Disorders	**13 (6.1)**	**20 (7.1)**	**28 (8.1)**
Decreased Appetite	4 (1.9)	6 (2.1)	7 (2.0)
Hyperuricaemia	3 (1.4)	4 (1.4)	5 (1.4)
Tumour Lysis Syndrome	4 (1.9)	6 (2.1)	11 (3.2)

System Organ Class / Preferred Term	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
Respiratory, Thoracic and Mediastinal Disorders	**27 (12.6)**	**31 (11.1)**	**37 (10.7)**
Dyspnoea	9 (4.2)	9 (3.2)	11 (3.2)
IDH Differentiation Syndrome *	14 (6.5)	18 (6.4)	22 (6.4)

TEAs associated with the mechanism of action

The TEAEs of enasidenib related differentiation syndrome (IDH differentiation syndrome), leukocytosis and tumor lysis syndrome as well as gastrointestinal disorders and hyperbilirubimemia were determined as ADRs associated with the mechanism of action of enasidenib. The current sections focus on the

assessments of these ADRs. In addition, the TEAEs resulting in renal toxicity, cardiac toxicity and Blood and Lymphatic System Disorders are going to be assessed.

IDH Differentiation syndrome is a life-threatening drug related adverse event comparable with the "retinoid acid syndrome" described retinoid acid (e.g. for Vesanoid) in treatment of acute promyelocytic leukemia (APL). It is characterized by rapid weight gain, pleural and pericardial effusions, peripheral edema, respiratory distress, and fever. Additional it can be accompanied by leukocytosis and TLS.

The incidences of the TEAE of IDH differentiation syndrome are presented in Table OVsaf05.

Table OVsaf05: Summary of Investigator-reported IDH Differentiation Syndrome for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

TEAE Category	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
TEAE	28 (13.1)	34 (12.1)	39 (11.3)
Related TEAE	27 (12.6)	33 (11.8)	38 (11.0)
Grade 3	14 (6.5)	17 (6.1)	20 (5.8)
Grade 4	0	1 (0.4)	2 (0.6)
Grade 3 or 4 TEAE	14 (6.5)	18 (6.4)	22 (6.4)
Related Grade 3 or 4 TEAE	14 (6.5)	18 (6.4)	22 (6.4)
TESAE	16 (7.5)	21 (7.5)	25 (7.2)
Related TESAE	16 (7.5)	21 (7.5)	25 (7.2)
Grade 5 TEAE	0	0	0
TEAE Leading to Discontinuation of Study Drug	0	2 (0.7)	2 (0.6)
Related TEAE Leading to Discontinuation of Study Drug	0	2 (0.7)	2 (0.6)
TEAE Leading to Study Drug Dose Modification or Reduction	0	0	0
TEAE Leading to Study Drug Dose Interruption	8 (3.7)	12 (4.3)	15 (4.3)

AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, IDH = isocitrate dehydrogenase, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, R/R AML = relapsed or refractory acute myeloid leukemia, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.

Data represent number (%) of subjects with at least 1 event. Events of IDH differentiation syndrome are based on the MedDRA PT of acute promyelocytic leukemia differentiation syndrome. TEAEs were defined as any AE that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related. CTCAE Grade version 4.03.

[a] For 1 subject, treatment was actually stopped due to fatal staphylococcal sepsis, contracted during the recovery period for IDH differentiation syndrome.

Data as of the 01 Sep 2017 cutoff.

Source: Table 14.3.1.9.6 of AG221-C-001, Table 14.3.1.9.7 of AG221-C-001, Table 14.3.1.2.8.1 of AG221-C-001, Table 14.3.1.2.8.2 of AG221-C-001.

No definitive risk factors for IDH differentiation syndrome have been individuated; with the only exception of a high count of bone marrow blasts (see the Table OVsaf06).

Table OVsaf06: Summary of baseline Disease characteristics by differentiation Syndrome

Table 14.3.1.33.2
Summary of Baseline Disease Characteristics by Differentiation Syndrome
by Malignancy Types and Overall - Combined Phase 1/2 (Safety Analysis Set)(

	R/R AML		
Parameter	DS (N=34) n (%)	Non-DS (N=246) n (%)	Overall (N=280) n (%)
Age (years)			
Median	69.5	68.0	68.0
Min, Max	38.0, 80.0	19.0, 100.0	19.0, 100.0
Age Categories (years)			
< 65	13 (38.2)	92 (37.4)	105 (37.5)
>=65-<75	16 (47.1)	93 (37.8)	109 (38.9)
>=75	5 (14.7)	61 (24.8)	66 (23.6)
Sex			
Female	14 (41.2)	113 (45.9)	127 (45.4)
Male	20 (58.8)	133 (54.1)	153 (54.6)
ECOG			
0	10 (29.4)	52 (21.1)	62 (22.1)
1	21 (61.8)	149 (60.6)	170 (60.7)
2	3 (8.8)	44 (17.9)	47 (16.8)
Missing	0 (0.0)	1 (0.4)	1 (0.4)
IDH2 Mutation			
R172	9 (26.5)	61 (24.8)	70 (25.0)
R140	25 (73.5)	184 (74.8)	209 (74.6)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	1 (0.4)	1 (0.4)
Number of Prior Anti-Cancer Regimens			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	20 (58.8)	105 (42.7)	125 (44.6)
2-5	14 (41.2)	139 (56.5)	153 (54.6)
>5	0 (0.0)	2 (0.8)	2 (0.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin (g/dL)			
< 10	27 (79.4)	173 (70.3)	200 (71.4)
>= 10	7 (20.6)	72 (29.3)	79 (28.2)

Missing	0 (0.0)	1 (0.4)	1 (0.4)
Platelets (x 10^9/L)			
< 10	2 (5.9)	9 (3.7)	11 (3.9)
10 - < 40	14 (41.2)	114 (46.3)	128 (45.7)
>= 40	18 (52.9)	122 (49.6)	140 (50.0)
Missing	0 (0.0)	1 (0.4)	1 (0.4)
WBC (x 10^9/L)			
<2	11 (32.4)	108 (43.9)	119 (42.5)
2 to < 5	9 (26.5)	59 (24.0)	68 (24.3)
5 to < 10	5 (14.7)	24 (9.8)	29 (10.4)
10 to < 50	9 (26.5)	47 (19.1)	56 (20.0)
>= 50	0 (0.0)	7 (2.8)	7 (2.5)
Missing	0 (0.0)	1 (0.4)	1 (0.4)
Bone Marrow Blast %			
<30%	4 (11.8)	79 (32.1)	83 (29.6)
>=30 - <50%	13 (38.2)	47 (19.1)	60 (21.4)
>=50 - <70%	8 (23.5)	43 (17.5)	51 (18.2)
>=70%	9 (26.5)	73 (29.7)	82 (29.3)
Missing	0 (0.0)	4 (1.6)	4 (1.4)
Lactate Dehydrogenase (LDH)			
<=ULN	17 (50.0)	157 (63.8)	174 (62.1)
>ULN - <2ULN	12 (35.3)	58 (23.6)	70 (25.0)
>=2ULN	5 (14.7)	30 (12.2)	35 (12.5)
Missing	0 (0.0)	1 (0.4)	1 (0.4)
Creatinine Clearance (mL/min)			
>=60	29 (85.3)	192 (78.0)	221 (78.9)
>=45 to <60	4 (11.8)	36 (14.6)	40 (14.3)
>=30 to <45	1 (2.9)	15 (6.1)	16 (5.7)
<30	0 (0.0)	2 (0.8)	2 (0.7)
Missing	0 (0.0)	1 (0.4)	1 (0.4)
Cytogenetic Risk Status			
Intermediate-Risk	16 (47.1)	125 (50.8)	141 (50.4)
Poor-Risk	8 (23.5)	61 (24.8)	69 (24.6)
Failure	3 (8.8)	5 (2.0)	8 (2.9)
Missing	7 (20.6)	55 (22.4)	62 (22.1)
Prior Hydroxyurea use			
None	29 (85.3)	206 (83.7)	235 (83.9)
Discontinued Prior to First Dose	1 (2.9)	6 (2.4)	7 (2.5)
Continued After First Dose	4 (11.8)	34 (13.8)	38 (13.6)
Best Response			
CR	6 (17.6)	47 (19.1)	53 (18.9)
Non-CR responder	11 (32.4)	47 (19.1)	58 (20.7)
Non-responder	16 (47.1)	136 (55.3)	152 (54.3)
Missing	1 (2.9)	16 (6.5)	17 (6.1)
Time to Best Response			
<2 cycles	0 (0.0)	7 (2.8)	7 (2.5)
>=2 - <4 cycles	5 (14.7)	29 (11.8)	34 (12.1)
>=4 cycles	12 (35.3)	58 (23.6)	70 (25.0)
Non-responder	16 (47.1)	136 (55.3)	152 (54.3)
Missing	1 (2.9)	16 (6.5)	17 (6.1)

Treatment with enasidenib can induce myeloid proliferation, which can manifest as increase in WBC count without evidence of infection or clinical signs of IDH differentiation syndrome. Incidence of TEAEs of *non-infectious leukocytosis* in Study AG221-C-001 is presented in Table OVsafS07:

Table OVsaf07: Summary of Treatment-emergent Adverse Events of Non-Infectious Leukocytosis or White Blood Cell Increase for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

TEAE Category	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
TEAE	29 (13.6)	44 (15.7)	53 (15.4)
Related TEAE	9 (4.2)	13 (4.6)	16 (4.6)
Grade 3 or 4 TEAE	12 (5.6)	17 (6.1)	19 (5.5)
Related Grade 3 or 4 TEAE	3 (1.4)	5 (1.8)	6 (1.7)
TESAE	14 (6.5)	20 (7.1)	22 (6.4)
Related TESAE	3 (1.4)	6 (2.1)	8 (2.3)
Grade 5 TEAE	1 (0.5)	1 (0.4)	1 (0.3)
TEAE Leading to Discontinuation of Study Drug	2 (0.9)	3 (1.1)	4 (1.2)
Related TEAE Leading to Discontinuation of Study Drug	1 (0.5)	1 (0.4)	2 (0.6)
TEAE Leading to Study Drug Dose Modification or Reduction	0 (0.0)	1 (0.4)	1 (0.3)
TEAE Leading to Study Drug Dose Interruption	4 (1.9)	8 (2.9)	9 (2.6)

CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, R/R AML = relapsed or refractory acute myeloid leukemia, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event, WBC = white blood cell.

Data represent number (%) of subjects with at least 1 event.

Non-infectious leukocytosis or WBC increase is defined as the event without occurrence of infection and infestations or febrile neutropenia within ± 7 days of the occurrence of leukocytosis/WBC increase. Leukocytosis event is defined as preferred term = leukocytosis; WBC increase event is defined as preferred term=white blood cell count increased. TEAEs were defined as any AE that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related. CTCAE Grade version 4.03. Data cutoff date: 01 Sep 2017.

Data as of the 01 Sep 2017 cutoff.

Source: Table 14.3.1.37.1 of AG221-C-001, Table 14.3.1.37.2 of AG221-C-001.

For the total R/R AML population, and by dose group, there were no substantial differences in baseline or disease characteristics among subjects who experienced non-infectious leukocytosis or WBC count increased versus those who did not, except that a higher proportion of subjects who had these events had higher WBC count and bone marrow blast count (%) at baseline.

Enasidenib-treated patients may develop *tumor lysis syndrome* caused by rapid degradation of WBC infiltrates in the peripheral tissues following resolution of IDH differentiation syndrome. The TEAEs attributed to treatment with enasidenib usually manifested within the first 3 months.

The incidence of TEAEs of tumor lysis syndrome in Study AG221-C-001 is presented in Table OVsaf08.

Table OVsaf08: Summary of Treatment-emergent Adverse Events of Tumor Lysis Syndrome for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

TEAE Category	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
TEAE	13 (6.1)	19 (6.8)	27 (7.8)
Related TEAE	5 (2.3)	7 (2.5)	13 (3.8)
Grade 3	10 (4.7)	15 (5.4)	22 (6.4%)
Grade 4	1 (0.5)	2 (0.7)	2 (0.6)
Related Grade 3 or 4 TEAE	4 (1.9)	6 (2.1)	11 (3.2)
TESAE	10 (4.7)	15 (5.4)	21 (6.1)
Related TESAE	3 (1.4)	5 (1.8)	9 (2.6)
Grade 5 TEAE	1 (0.5)	1 (0.4)	1 (0.3)
TEAE Leading to Discontinuation of Study Drug	2 (0.9)	2 (0.7)	2 (0.6)
Related TEAE Leading to Discontinuation of Study Drug	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Study Drug Dose Modification or Reduction	0 (0.0)	0 (0.0)	1 (0.3)
TEAE Leading to Study Drug Dose Interruption	1 (0.5)	4 (1.4)	6 (1.7)

AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, R/R AML = relapsed or refractory acute myeloid leukemia, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.
Data represent number (%) of subjects with at least 1 event. Events of tumor lysis syndrome are based on the PT of tumor lysis syndrome. TEAEs were defined as any AE that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related. CTCAE version 4.03.
Data as of the 01 Sep 2017 cutoff.
Source: Table 14.3.1.2.8.1, Table 14.3.1.2.8.2, Table 14.3.1.9.6, and Table 14.3.1.9.7 of AG221-C-001.

Through this case review of TLS, the Applicant concluded that IDH differentiation syndrome-induced migration of leukocytes may be followed by rapid degradation of WBC infiltrates into the peripheral tissues, which may lead to signs and symptoms of TLS.

While causality of *gastrointestinal disorders* (overall common in this patient population) is hard to ascertain in an uncontrolled study, the nonclinical toxicology data, short time to onset of gastrointestinal TEAEs, as well as common attribution of TEAE causality to enasidenib by the investigators, suggest a potential gastrointestinal tract irritation associated with enasidenib administration.

The incidence of TEAEs of gastrointestinal disorders in Study AG221-C-001 is presented in Table OVsaf09:

Table OVsaf09: Table saf12: Summary of Gastrointestinal TEAEs of Abdominal Pain, Nausea and Vomiting, Diarrhea, Decreased Appetite, and Dysgeusia for All Subjects Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

TEAE Category	All Subjects Combined Phase 1/2 (N = 345)				
	Abdominal Pain[a]	Nausea and Vomiting[b]	Diarrhea[c]	Decreased Appetite[d]	Dysgeusia[e]
TEAE	74 (21.4)	193 (55.9)	144 (41.7)	117 (33.9)	43 (12.5)
Related TEAE	12 (3.5)	110 (31.9)	52 (15.1)	61 (17.7)	36 (10.4)
Grade 3 or 4 TEAE	5 (1.4)	19 (5.5)	15 (4.3)	15 (4.3)	0
Related Grade 3-4 TEAE	1 (0.3)	8 (2.3)	3 (0.9)	7 (2.0)	0
Grade 5 TEAE	0	0	0	0	0
TESAE	8 (2.3)	18 (5.2)	13 (3.8)	8 (2.3)	0
Related TESAE	1 (0.3)	10 (2.9)	3 (0.9)	5 (1.4)	0
TEAE leading to Discontinuation of Study Drug	0	1 (0.3)	1 (0.3)	0	0
Related TEAE leading to Discontinuation of Study Drug	0	0	0	0	0
Leading to Study Drug Dose Modification or Reduction	0	5 (1.4)	2 (0.6)	3 (0.9)	0
Leading to Study Drug Dose Interruption	5 (1.4)	8 (2.3)	2 (0.6)	2 (0.6)	0

AE = adverse events, HLT = higher level term, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.
Data represent number (%) of subjects with at least 1 event. TEAEs were defined as any AEs that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by investigator to be related to study drug.
[a] Abdominal pain based on the HLT gastrointestinal and abdominal pains (excluding oral and throat).
[b] Nausea and vomiting based on the HLT nausea and vomiting symptoms.
[c] Diarrhea based on the MedDRA PTs of diarrhoea, diarrhoea haemorrhagic.
[d] Decreased appetite based on the MedDRA PT of decreased appetite
[e] Dysgeusia includes taste and smell disorders.
Data as of the 01 Sep 2017 cutoff.
Source: Table 14.3.1.2.8.2 of AG221-C-001.

No dose-dependent trend was noted for TEAEs of nausea, diarrhea, vomiting, decreased appetite and dysgeusia. For the majority of subjects, the events were reported during the first or second cycle of treatment.

In vitro metabolism studies have shown that enasidenib inhibits UGT1A1, the enzyme responsible for the metabolism of bilirubin (condition similar to Gilbert's syndrome). This observation was also confirmed in in vivo nonclinical studies where an increase in serum bilirubin was noted in all species tested.

In clinical studies with enasidenib, TEAEs associated with bilirubin elevation were very common and dose-dependent increases were observed for total and indirect bilirubin and, to a lesser degree, for direct bilirubin.

The incidence of TEAEs of *Biliary system related investigations* in Study AG221-C-001 is presented in Table OVsaf10:

Table OVsaf10: Summary of Treatment-emergent Adverse Events from the MedDRA SMQ Biliary System Related Investigations, Signs and Symptoms, for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
TEAE	80 (37.4)	111 (39.6)	139 (40.3)
Blood Bilirubin Increased	65 (30.4)	92 (32.9)	117 (33.9)
Hyperbilirubinaemia	19 (8.9)	26 (9.3)	31 (9.0)
Jaundice	2 (0.9)	4 (1.4)	5 (1.4)
Bilirubin Conjugated Increased	1 (0.5)	2 (0.7)	3 (0.9)
Related TEAE	71 (33.2)	97 (34.6)	120 (34.8)
Grade 3-4 TEAE	23 (10.7)	36 (12.9)	49 (14.2)
Related Grade 3-4 TEAE	15 (7.0)	27 (9.6)	36 (10.4)
TESAE	3 (1.4)	6 (2.1)	8 (2.3)
Related TESAE	2 (0.9)	5 (1.8)	6 (1.7)
Grade 5 TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Related Grade 5 TEAE	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Discontinuation of Study Drug	3 (1.4)	3 (1.1)	3 (0.9)
Related TEAE Leading to Discontinuation of Study Drug	3 (1.4)	3 (1.1)	3 (0.9)
TEAE Leading to Study Drug Dose Modification or Reduction	1 (0.5)	5 (1.8)	5 (1.4)
TEAE Leading to Study Drug Dose Interruption	9 (4.2)	15 (5.4)	21 (6.1)

AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, R/R AML = relapsed or refractory acute myeloid leukemia, SMQ = standardized MedDRA query, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.
Data represent number (%) of subjects with at least 1 event. Preferred Terms were coded using the MedDRA dictionary version 20.0. TEAEs are based on the MedDRA SMQ Biliary System Related Investigations, Signs and Symptoms (narrow scope). TEAEs were defined as any AE that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related. CTCAE Grade version 4.03.
Data as of the 01 Sep 2017 cutoff.
Source: Table 14.3.1.30.9 of AG221-C-001, Table 14.3.1.30.7 of AG221-C-001, Table 14.3.1.30.4 of AG221-C-001, and Table 14.3.1.30.5 of AG221-C-001.

In addition, table OVsaf11 presents post-baseline Changes of Interest in Hepatic Function Laboratory Parameters:

Table OVsaf11: Post-baseline Changes of Interest in Hepatic Function Laboratory Parameters for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

Parameter	Criteria	R/R AML 100 mg Dose (n = 214)		All R/R AML (n = 280)		All Subjects (N = 345)	
		Any Visit	Last Visit	Any Visit	Last Visit	Any Visit	Last Visit
ALT	≥ 3x ULN and < 5x ULN	18 (8.4)	4 (1.9)	21 (7.5)	4 (1.4)	24 (7.0)	4 (1.2)
	≥ 5x ULN and < 8x ULN	3 (1.4)	0	3 (1.1)	0	6 (1.7)	0
	≥ 8x ULN	2 (0.9)	1 (0.5)	3 (1.1)	1 (0.4)	3 (0.9)	1 (0.3)
AST	≥ 3x ULN and < 5x ULN	11 (5.1)	2 (0.9)	14 (5.0)	2 (0.7)	19 (5.5)	3 (0.9)
	≥ 5x ULN and < 8x ULN	2 (0.9)	0	3 (1.1)	0	4 (1.2)	0
	≥ 8x ULN	1 (0.5)	1 (0.5)	3 (1.1)	1 (0.4)	3 (0.9)	1 (0.3)
Total bilirubin	≥ 2x ULN	84 (39.3)	52 (24.3)	115 (41.1)	67 (23.9)	141 (40.9)	84 (24.3)
	≥ 3x ULN	37 (17.3)	16 (7.5)	52 (18.6)	23 (8.2)	67 (19.4)	31 (9.0)
Total bilirubin ≥ 2x ULN and ALT ≥ 3x ULN[a]	ALT ≥ 3x ULN and < 5x ULN	6 (2.8)	1 (0.5)	8 (2.9)	1 (0.4)	9 (2.6)	1 (0.3)
	ALT ≥ 5x ULN and < 8x ULN	2 (0.9)	0	2 (0.7)	0	3 (0.9)	0
	ALT ≥ 8x ULN	1 (0.5)	1 (0.5)	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Total bilirubin ≥ 2x ULN and AST ≥ 3x ULN[a]	AST ≥ 3x ULN and < 5x ULN	8 (3.7)	1 (0.5)	9 (3.2)	1 (0.4)	10 (2.9)	2 (0.6)
	AST ≥ 5x ULN and < 8x ULN	1 (0.5)	0	1 (0.4)	0	1 (0.3)	0
	AST ≥ 8x ULN	1 (0.5)	1 (0.5)	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)

ALT = alanine aminotransferase, AML = acute myelogenous leukemia, AST = aspartate aminotransferase, R/R = relapsed or refractory acute myeloid leukemia, ULN = upper limit of normal.

[a] Total bilirubin ≥ 2x ULN and ALT or AST ≥ 3x ULN concurrent and within 1 cycle of total bilirubin elevation and at any time after start of treatment.

Data represent number (%) of subjects.

Data as of the 01 Sep 2017 cutoff.

Source: Table 14.3.5.10.6 of AG221-C-001 and Table 14.3.5.10.7 of AG221-C-001.

As shown in Table OVsaf11, elevations in transaminases and bilirubin reaching Hy's law level. However, with regard to the presented narratives (please be referred to the clinical summary of safety) those events were transient and mostly associated with non-hepatic severe and serious TEAEs and their treatments.

Genetic testing for UGTA1A gene mutation was mandatory for subject enrolled in pivotal study AG221-C-001 (protocol amendment n. 4). A total of 65 subjects were tested for UGT1A1 allele mutation (Gilbert's syndrome): 16 were homozygous, 27 heterozygous and the remaining 22 were wild-type non-mutant. Despite the Applicants did not find any significant differences in terms of all grades bilirubin TEAE (37.5% vs 29.6% vs 36.4%, respectively), a significant higher number of grade ≥3 TEAE was observed in subjects with allele mutation vs wild type (homozygous: 12.5%, heterozygous: 11.1%, wild-type: 0). However, elevation of bilirubin > 3 times ULN sustained for two weeks or more was managed by enasidenib dose reduction to 50 mg QD. Therefore, no restriction of starting dose is recommended in patients with UGT1A1 gene mutation.

Adverse reactions associated with the enasidenib mechanism of action, such as IDH differentiation syndrome and tumor lysis syndrome, may lead to *acute renal failure* with transient increase in serum creatinine, while volume depletion due to gastrointestinal disturbances produces pre-renal failure. In

addition acute renal failure is common in patients with AML, with > 40% of patients with hematologic malignancies admitted to the intensive care unit demonstrating signs of renal injury (Luciano, 2014). A large proportion of patients with hematologic malignancies treated for sepsis develop renal failure (Harris, 1991). Overall, 104 (30.1%) subjects had at least 1 Standardized MedRA query SMQ) TEAE. However, most patients with these TEAE had events that were assessed as unrelated to study drug by the investigators.

Cardiac safety was evaluated by using the SMQ Torsade de Points/QT Prolongation, as resumed in TableOVsaf12.

Table OVsaf12: Treatment-emergent Adverse Events from the SMQ Torsade de Pointes / QT Prolongation for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of StudyAG221-C-001 (Safety Analysis Set)

Preferred Term	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
Subject with at least 1 SMQ TEAE	24 (11.2)	32 (11.4)	42 (12.2)
Electrocardiogram QT prolonged	12 (5.6)	15 (5.4)	22 (6.4)
Syncope	6 (2.8)	9 (3.2)	12 (3.5)
Cardiac arrest	5 (2.3)	6 (2.1)	6 (1.7)
Loss of consciousness	2 (0.9)	3 (1.1)	3 (0.9)
Ventricular tachycardia	1 (0.5)	2 (0.7)	2 (0.6)
Sudden death	0 (0.0)	0 (0.0)	1 (0.3)

AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, R/R AML = relapsed or refractory acute myeloid leukemia, SMQ = standardized MedDRA query, TEAE = treatment-emergent adverse event.
Data represent number (%) of subjects. TEAEs are based on the MedDRA SMQ Torsade de pointes / QT Prolongation (broad scope). Preferred term was coded using the MedDRA dictionary version 20.0. Preferred term is sorted in descending order of frequency in overall column. A subject is counted only once for multiple events within preferred term. TEAEs were defined as any AEs that began or worsened on or after the start of study drug through 28 days after the last dose of study drug.
Data as of the 01 Sep 2017 cutoff.
Source: Table 14.3.1.27.4 of AG221-C-001 and Table 14.3.1.27.5 of AG221-C-001.

Overall, in 22 cases (6.4%) a TEAE of QT prolongation was reported. From a retrospective analysis, it was shown that all patients with QT prolongation had prolongation evident through baseline ECG analysis or had other concurrent factors affecting QT interval (i.e. concomitant administration of medication with known QT prolonging interval, electrolytes abnormalities). In particular a) thirty-seven patients had received concomitant medications known for their QT prolongation; b) thirteen patients had concurrent electrolytes abnormalities that could have influenced QT interval prolongation; c) seven patients had baseline prolonged QT interval; d) five patients had a pacemaker (QT interval prolongation not evaluable); e) one patient experienced QT increase (> 60 msec from baseline) during cycle 5 at the time of disease progression. Only one grade 3 TEAE of syncope was evaluated as treatment-related in a patient with concomitant multiple sclerosis. Cardiac arrest was reported in 6 cases (1.7%) and in 2.3% among R/R AML patients treated with Enasidenib 100 mg, but all cases were defined as not treatment-related by the investigators. Two cases of ventricular tachycardia were defined as non-treatment-related. Central ECG assessment showed no significant changes in heart rate and any of the ECG intervals during Enasidenib treatment.

Treatment with enasidenib seems to reduce TEAEs in the SOC of *blood and lymphatic system disorders* and the SOC of *infections* over time. As presented in efficacy sections patients who achieved a response had reduced incidence of grade 3/4 infection, bleeding, and febrile neutropenia during the periods of response compared with non-responders.

However, infections were frequently observed during treatment with Enasidenib. TEAEs within the SOC Infections and Infestations were reported for 248 subjects (71.9%) and resumed in Table OVsaf13.

Table OVsaf13: Summary of Treatment-emergent Adverse Events from the SOC Infections and Infestations for All Subjects and Subjects with R/R AML by Total Daily Dose of 100 mg and Overall in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

TEAE Categories	R/R AML 100 mg Dose (n=214)	All R/R AML (n=280)	All Subjects (N=345)
TEAE	158 (73.8)	206 (73.6)	248 (71.9)
Related TEAE	12 (5.6)	16 (5.7)	20 (5.8)
Grade 3 TEAE	69 (32.2)	90 (32.1)	114 (33.0)
Grade 4 TEAE	24 (11.2)	31 (11.1)	33 (9.6)
Grade 3 or 4 TEAE	17 (50.0)	142 (50.7)	173 (50.1)
Related Grade 3 or 4 TEAE	5 (2.3)	7 (2.5)	7 (2.0)
TESAE	103 (48.1)	138 (49.3)	166 (48.1)
Related TESAE	4 (1.9)	6 (2.1)	7 (2.0)
Grade 5 TEAE	15 (7.0)	23 (8.2)	29 (8.4)
Related Grade 5 TEAE	0	0	0
TEAE Leading to Discontinuation of Study Drug	9 (4.2)	12 (4.3)	15 (4.3)
TEAE Leading to Study Drug Dose Modification or Reduction	0	2(0.7)	2 (0.6)
TEAE Leading to Study Drug Dose Interruption	26 (12.1)	41 (14.6)	49 (14.2)

AE = adverse event, AML = acute myeloid leukemia, CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, R/R = relapsed or refractory acute myeloid leukemia, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.
Data represent number (%) of subjects with at least 1 event. TEAEs were defined as any AE that began or worsened on or after the start of study drug through 28 days after the last dose of study drug. Related = suspected (possibly or probably) by the investigator to be related. CTCAE Grade version 4.03. Data cutoff: 14 Oct 2016
Source: Table 14.3.1.3.7 of AG221-C-001, Table 14.3.1.3.9 of AG221-C-001, Table 14.3.1.5.7 of AG221-C-001, Table 14.3.1.5.9 of AG221-C-001, Table 14.3.1.9.6 of AG221-C-001, Table 14.3.1.9.7 of AG221-C-001, Table 14.3.1.10.6 of AG221-C-001, Table 14.3.1.10.7 of AG221-C-001, Table 14.3.1.12.7 of AG221-C-001, Table 14.3.1.12.9 of AG221-C-001, Table 14.3.1.14.6 of AG221-C-001, Table 14.3.1.14.7 of AG221-C-001, Table 14.3.1.15.6 of AG221-C-001, Table 14.3.1.15.7 of AG221-C-001, Table 14.3.1.17.6 of AG221-C-001, Table 14.3.1.17.7 of AG221-C-001, Table 14.3.1.19.6 of AG221-C-001, Table 14.3.1.19.7 of AG221-C-001, Table 14.3.1.21.6 of AG221-C-001, Table 14.3.1.21.7 of AG221-C-001, Table 14.3.1.22.7 of AG221-C-001.

The more frequent TEAE reported were pneumonia (21.7%), sepsis (15.4%) and lung infections (11.3%) and in 106 cases (30.7%) these TEAE were associated to that of febrile neutropenia. Severe infections were predominantly reported in subjects not responding to study treatment and infectious complications as well as febrile neutropenia tended to decline on treatment after two cycles and with continued treatment. However, our detailed analysis of TEAE within SOC Infections and Infestations by cycle revealed that there was a significant incidence of grade 3-4 TEAE in advanced phase of treatment (cycle 10 phase 1-2: 9.5%; cycle 10 phase 2: 14.3%).

Serious adverse events and deaths

A total of 92 (26.7%) subjects had at least 1 suspected treatment-related TESAE. The SOCs for which most subjects experienced a suspected treatment-related TESAE were Respiratory, Thoracic and Mediastinal Disorders (10.4%), Blood and Lymphatic System Disorders (8.4%), Gastrointestinal Disorders (4.9%), and Metabolism and Nutrition Disorders (4.6% each). The most frequently reported suspected treatment-related TESAEs (occurring in ≥ 2% of subjects overall) were IDH differentiation syndrome (7.2%), leukocytosis (4.3%), tumor lysis syndrome, febrile neutropenia and nausea (2.6% each), and dyspnea (2.0%).

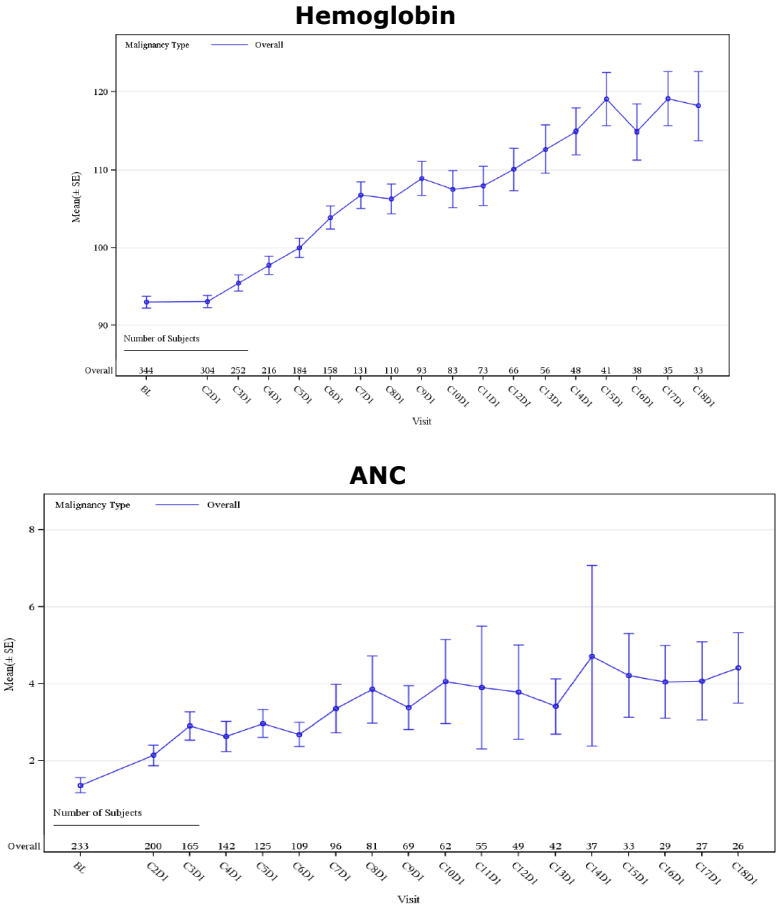
There were a total of 121 (35.1%) on-treatment all-cause deaths (ie, death for any cause within 28 days of the last dose of enasidenib). The causes of death reported in ≥ 1% of subjects were disease progression (7.5%), AML (5.5%), and complications of the underlying hematologic malignancy, mainly

multiple organ dysfunction syndromes (2.0%), infection (pneumonia [1.4%] and sepsis [4.3%]) and respiratory failure (3.8%).

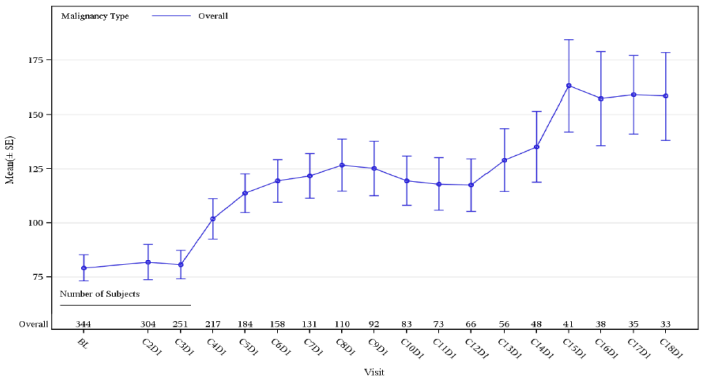
Laboratory findings

Haemoglobin, ANC, and platelets over time for all subjects are presented in Figure OVsaf01.

Figure OVsaf01: Mean (± SD) of Hemoglobin Concentration (g/L), ANC Concentration (109/L), and Platelet Concentration (109/L), by Visit up to Cycle 18 for All Subjects in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)



Platelets



The Applicants claimed that the median changes in hemoglobin, neutrophils and platelets (associated with decreasing needs for transfusions) values do not indicate a risk of myelosuppression in patients receiving Enasidenib

Mean changes from baseline in chemistry parameters from baseline by cycle through Cycle 6 Day 1 are summarized in Table OVsaf14.

Table OVsaf14: Mean Changes in Chemistry Parameters by Cycle through Cycle 6 Day 1 for All Subjects in the Combined Phase 1/2 of Study AG221-C-001 (Safety Analysis Set)

Parameter (unit)	Baseline Value [N]	Mean Change from Baseline [Number of Subjects]				
		C2D1	C3D1	C4D1	C5D1	C6D1
Albumin (g/L)	37.5 [344]	-2.0 [299]	-0.6 [244]	-1.3 [215]	0.3 [180]	1.1 [157]
Alkaline phosphatase (U/L)	96.8 [344]	0.1 [298]	0.7 [248]	9.3 [215]	6.8 [182]	4.4 [158]
ALT (U/L)	29.5 [344]	-2.7 [300]	-4.4 [249]	-2.6 [216]	0.5 [182]	-1.5 [158]
AST (U/L)	26.8 [343]	0.6 [294]	-1.9 [247]	0.7 [210]	0.1 [182]	-0.6 [156]
Amylase (U/L)	53.71 [336]	-2.80 [269]	2.01 [231]	0.28 [199]	-0.28 [165]	0.37 [149]
Direct bilirubin (µmol/L)	3.33 [329]	2.42 [264]	2.67 [225]	2.47 [192]	2.17 [165]	2.14 [147]
Total bilirubin (µmol/L)	10.82 [343]	13.61 [298]	14.44 [249]	13.98 [212]	12.88 [181]	13.61 [157]
Indirect bilirubin (µmol/L)	6.18 [299]	8.02 [229]	9.36 [199]	8.37 [166]	8.49 [145]	8.89 [131]
BUN (mmol/L)	6.296 [344]	0.717 [300]	0.779 [250]	0.495 [216]	0.671 [182]	0.619 [158]
Calcium (mmol/L)	2.240 [344]	-0.114 [302]	-0.099 [249]	-0.120 [215]	-0.111 [181]	-0.097 [158]
Creatine kinase (U/L)	46.65 [333]	-0.55 [264]	23.15 [220]	2.87 [193]	-0.71 [161]	-3.70 [145]
Chloride (mmol/L)	103.5 [344]	0.3 [302]	-0.4 [249]	0.2 [215]	0.2 [182]	0.2 [158]
Carbon dioxide/ bicarbonate (mmol/L)	26.5 [337]	-0.7 [295]	-0.8 [242]	-1.1 [208]	-0.7 [177]	-0.6 [155]
Serum creatinine (µmol/L)	78.21 [344]	12.14 [302]	10.93 [250]	11.21 [216]	8.12 [182]	8.64 [158]
Glucose (mmol/L)	6.716 [344]	0.436 [300]	0.317 [248]	0.449 [216]	0.028 [181]	0.081 [158]
Potassium (mmol/L)	4.04 [344]	-0.18 [301]	-0.13 [249]	-0.13 [213]	-0.07 [182]	-0.11 [158]
LDH (U/L)	404.1 [344]	82.9 [294]	30.4 [247]	19.5 [213]	13.5 [179]	-9.1 [156]
Lipase (U/L)	42.53 [337]	1.34 [275]	3.68 [228]	2.45 [195]	0.24 [162]	-5.66 [148]
Phosphorus (mmol/L)	1.243 [343]	0.065 [295]	0.061 [248]	0.062 [214]	0.083 [179]	0.116 [156]
Sodium (mmol/L)	138.8 [344]	-0.1 [302]	-0.2 [249]	0.0 [215]	0.2 [181]	0.4 [158]
Uric acid (µmol/L)	278.3 [342]	58.5 [288]	60.7 [239]	55.8 [210]	48.0 [178]	60.4 [153]

Coagulation studies

Mean changes from baseline to cycle 6 in all subjects were small for activated partial thromboplastin time (range of mean: 0.65 to -1.19 sec), international normalized ratio (range of mean: 0.122 to -0.044), and prothrombin time (range of mean: -0.46 to -1.88 sec), not suggesting any safety concern.

Safety in special populations

Evaluation of intrinsic factors is primarily based on the combined Phase 1/2 population of Study AG221-C-001. Although a subgroup analysis was performed in Study AG221-C-003 in solid tumours, the analysis was assessed as non-conclusive due to the small subject population. See Section 3.4 of Module 2.7.2 for additional discussion of intrinsic factors in terms of PK.

Age

In Study AG221-C-001, 23.5% of subjects were < 60 years old, 33.0% of subjects were < 65 years old, 67.0% of subjects were ≥ 65 years old, and 27.2% of subjects were ≥ 75 years old.

The incidence of subjects who reported at least 1 TEAE in each age group was as follows: 80 (98.8%) subjects < 60 years, 96 (100.0%) subjects ≥ 60 to < 70 years, 74 (100.0%) subjects ≥ 70 to < 75 years, and 94 (100.0%) subjects ≥ 75 years. There were no clinically relevant differences observed in the overall occurrence of TEAEs (all and treatment-related), Grade 3-4 TEAEs, Grade 5 TEAEs, TESAEs, or TEAEs that led to study drug discontinuation (all and treatment-related) by age group for subjects with R/R AML. Treatment-related TESAEs were reported for 24.0% of subjects ≥ 60 to < 70 years, 28.4% of subjects ≥ 70 to < 75 years, and 24.5% of subjects ≥ 75 years compared to 30.9% of subjects < 60 years.

Gender

A total of 201 (100.0%) male subjects and 143 (99.3%) female subjects reported at least 1 TEAE. There were no clinically relevant differences observed in the overall occurrence of TEAEs (all and treatment-related), Grade ¾ TEAEs (all and treatment-related), TESAEs (all and treatment-related), or TEAEs that led to study drug discontinuation or dose modification (all and treatment-related) by sex for subjects with R/R AML or for all subjects. However, Grade 5 TEAEs, discontinuation due to AEs, and TEAEs leading to dose modifications and reductions were reported more frequently for male than female subjects (27.4%, 22.4%, and 12.4% for men compared to 19.4%, 13.9%, and 4.9%, for women.)

Ethnicity

The incidence of subjects who reported at least 1 TEAE in each race group was as follows: 266 (99.6%) White subjects, 28 (100.0%) non-White subjects, 50 (100.0%) subjects with race not provided. There were no clinically relevant differences observed in the overall occurrence of TEAEs (all and treatment-related), Grade 3, 4, or 5 TEAEs (all and treatment-related), TESAEs, or TEAEs that led to dose modification or reduction (all and treatment-related) by race group for subjects with R/R AML or for all subjects. Treatment-related Grade 3 or 4 TEAEs were reported for 46.8% of White subjects and 32.1% of non-White subjects. Similarly, treatment-related TESAEs were reported for 27.0% of White subjects and 14.3% of non-White subjects. In general, ethnicity had no effect on the incidence or type of TEAEs. Assessment of individual TEAEs by race did not show clinically meaningful differences in the enasidenib safety profile. The relatively low number of non-White subjects (n=28) compared with the number of White subjects (n=267) in the overall SAS population limits the interpretation of adverse event data by ethnicity.

Results from Study AG-221-CP-001 indicated that there are no clinically relevant differences in exposures of enasidenib or AGI-16903 (a metabolite of enasidenib) between Japanese and White subjects under the currently tested dose levels (at a single dose of 50, 100, and 300 mg).

ECOG Performance status

79 (22.9%) subjects had a baseline ECOG performance status of 0, 204 (59.1%) subjects had a baseline performance status of 1, and 61 (17.7%) subjects had a baseline performance status of 2.

Overall for all subjects, higher ECOG performance status at baseline correlated with higher incidence of severe TEAEs. Specifically, for subjects with baseline ECOG performance status of 0, 1, and 2, the following were reported: Grade 3 or 4 TEAEs for 83.5%, 88.7%, and 98.4% of subjects, respectively; Grade 5 TEAEs for 16.5%, 25.0%, and 31.1% of subjects, respectively; TESAEs for 69.6%, 81.4%, and 91.8% of subjects, respectively; and TEAEs leading to discontinuation for 13.9%, 19.1%, and 24.6% of subjects, respectively. There were no clinically relevant differences from baseline observed in the overall occurrence of TEAEs (all and treatment-related), nor for other TEAE treatment-related categories.

Renal impairment

Study AG221-C-001 excluded subjects with creatinine clearance ≤ 40 mL/min at screening. In the combined Phase 1/2 population, baseline creatinine clearance ranged between 26.1 and 237.4 mL/min, with 26 (7.5%) subjects having a baseline creatinine clearance of < 45 mL/min, 54 (15.7%), subjects having a baseline creatinine clearance of 45 to < 60 mL/min and 264 (76.5%) subjects having a baseline creatinine clearance of ≥ 60 mL/min. There were no meaningful differences observed in the overall occurrence of TEAEs (all and treatment-related), Grade 3 or 4 (all and treatment-related), or Grade 5 TEAEs (all and treatment-related), TESAEs (all and treatment-related). However dose interruptions due to TEAEs were reported more often for subjects with a baseline creatinine clearance of < 45 mL/min (61.5%) compared with subjects with a baseline creatinine clearance of 45 to < 60 mL/min and subjects with a baseline creatinine clearance of ≥ 60 mL/min (53.7% and 44.3%, respectively). In addition in phase II part discontinuation of study drug due to TEAEs was reported more often for subjects with a baseline creatinine clearance of < 45 mL/min (50.0%) compared with subjects with a baseline creatinine clearance of 45 to < 60 mL/min and subjects with a baseline creatinine clearance of ≥ 60 mL/min (26.7% and 18.1%, respectively).

Hepatic impairment

The ongoing clinical studies excluded subjects with ALT or AST > 3x ULN. The percentage of subjects who had post-baseline ALT, AST, and total bilirubin values outside the normal ranges (ie, Grade ≥ 1) were as follows: ALT Grade 1, 2, 3, and 4 of 31.7%, 6.8%, 1.1%, and 0.4%, respectively; AST Grade 1, 2, 3, and 4 of 39.0%, 2.9%, 1.8%, and 0.4% respectively; and total bilirubin Grade 1, 2, 3, and 4 of 22.0%, 41.9%, 18.4%, and 0.4%, respectively. A HI-Study was not performed up till now.

Geographic region

AG221-C-001 study was conducted in two countries: US (n=294) and France (n=51). There were no clinically relevant differences observed in the overall occurrence of TEAEs (all and treatment-related), grade 3 or 4 TEAEs (all and treatment-related), treatment-related grade 5 TEAEs, TESAEs, TEAEs leading to discontinuation (all and treatment-related), and TEAEs leading to dose modification or reduction (all and treatment-related) by region for subjects with R/R AML or for all subjects. There were greater incidences among all subjects of grade 5 TEAEs and treatment-related TESAEs for subjects enrolled at the sites in France (33.3% and 41.2%) compared with subjects enrolled in sites in the US (22.4% and 24.1%). Similarly, among R/R AML subjects there were greater incidences of Grade 5 TEAEs and treatment-related TESAEs for subjects enrolled at sites in France (32.6% and 43.5%) compared with subjects enrolled in sites in the US (20.5% and 24.8%). For all subjects, the incidence of TEAEs that led to dose interruption was 27.5% for subjects enrolled at sites in France and 50.3% for subjects enrolled at sites in the US.

Use in pregnancy and lactation

There were no data on enasidenib administration in this patient population, being women pregnant or lactating not eligible to enrolled in any study.l

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Based on in vitro assessment, enasidenib and its major metabolite AGI-16903 have drug-drug interaction risk at clinical exposure as an inhibitor of concomitant medications that are sensitive to substrates of multiple cytochrome P450 (CYP) isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6), UGT1A1,

or the human transporters p-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporter (OAT) P1B1.

In a population PK analysis using data from subjects with advanced hematologic malignancies who had evaluable PK data in Study AG221-C-001, co-medications with CYP inhibitors were not significant covariates affecting enasidenib exposure (AG-221-MPK-001).

Discontinuation due to AES

A total of 65 (18.8%) subjects had at least 1 TEAE that led to permanent study drug discontinuation. The SOCs for which most subjects experienced an event were Infections and Infestations (4.3%), Respiratory, Thoracic and Mediastinal Disorders (3.8%), and Blood and Lymphatic System Disorders (3.5%). The most frequently reported TEAEs that led to discontinuation (occurring in ≥ 1.0% of subjects overall) were sepsis (2.6%), leukocytosis (2.0%), and respiratory failure (1.7%). Overall, the incidence of TEAEs leading to permanent discontinuation was similar across dose groups and in subjects with R/R AML versus the entire population of subjects with hematologic malignancies enrolled in this study.

A total of 16 (4.6%) subjects had at least 1 treatment-related TEAE that led to permanent study drug discontinuation, and no specific event occurred in more than 2 subjects. The events leading to discontinuation that occurred in 2 subjects each were as follows: leukocytosis, which were Grade 4 events for both subjects and considered to be non-infectious leukocytosis; thrombocytopenia (a Grade 3 and a Grade 4 event); blood alkaline phosphatase increased (a Grade 1 and Grade 3 event); blood bilirubin increased (a Grade 2 and Grade 3 event); and IDH differentiation syndrome (a Grade 2 and Grade 3 event). Treatment-related TEAEs that led to permanent study drug discontinuation in 1 subject each were Grade 4 bone marrow failure, Grade 5 cardiac tamponade, Grade 2 fatigue, Grade 5 acute hepatic failure, Grade 3 alanine aminotransferase increased, Grade 3 aspartate aminotransferase increased, Grade 3 bilirubin conjugated increased, Grade 4 platelet count decreased, Grade 3 confusional state, and Grade 3 rash. No dose dependency was observed for treatment-related TEAEs that led to permanent study drug discontinuation.

In subjects with R/R AML, 13 (4.6%) subjects discontinued due to a TEAE considered related to study drug. Overall, the proportion of subjects with treatment-related TEAEs leading to permanent discontinuation was similar across dose groups and in subjects with R/R AML versus the entire population of subjects with hematologic malignancies enrolled in this study.

A total of 26 (7.5%) subjects had at least 1 treatment-related TEAE that led to dose modification or reduction. The only treatment-related TEAEs that led to dose modification or reduction that occurred in ≥ 1.0% of subjects overall was nausea (1.2%).

Comparison of safety data from Study AG221-C-001 with historical controls

Comparison to Targeted Therapy: Selective Inhibition of IDH2 by Enasidenib versus Selective Inhibition of FLT3 by Gilteritinib in Relapsed or Refractory Acute Myeloid Leukemia

The comparison of the baseline characteristics are presented in table OVsaf15.

Table OVsaf15: Baseline Demographic and Disease Characteristics for Enasidenib-treated and Gilteritinib-treated Subjects

Parameter	Enasidenib R/R AML 100 mg Dose Safety Analysis Set (n=214)	Gilteritinib Safety Analysis Set (n=252)[a]
Age, Median(s) (Minimum, Maximum) (years)	68.0 (19, 100)	60 to 65 (47, 71)
Men, n (%)	109 (50.9)	129 (51.1)
Cytogenetic risk[b], n (%)		
Favorable	0	7 (2.8)
Intermediate	108 (50.5)	143 (56.7)
Adverse[c]	62 (29.0)	56 (22.2)
Previous Stem Cell Transplants, n (%)	29 (13.6)	73 (28.9)
Lines of previous treatment for AML[d], n (%)		
1	101 (47.2)	75 (29.8)
2	65 (30.4)	66 (26.2)
≥ 3	48 (22.4)	111 (44.0)

n = number, R/R AML = relapsed or refractory acute myeloid leukemia.
[a] Gilteritinib baseline characteristics reported by Perl et al are presented by dose cohort in Perl, 2017; the data are combined to provide a total for all subjects overall as well an average, where possible. The range of median age for the cohorts is provided: The median ages, by cohort, were 65, 62, 62, 60, 64, 64, and 64 years for the 20, 40, 80, 120, 200, 300, and 450 mg QD cohorts.
[b] Data are not available for some subjects.
[c] Enasidenib data are reported as "Poor risk" and "Failure" categories in Study AG221-C-001.

Grade 1-2 TEAEs reported with substantially higher frequency (approximately two times higher) in the enasidenib-treated subjects as compared to gilteritinib-treated subjects were recognized ADRs to enasidenib and included nausea, increased blood bilirubin, decreased appetite, leukocytosis, and IDH differentiation syndrome.

Grade 1-2TEAEs reported with substantially higher frequency (approximately two times higher) in the gilteritinib-treated subjects as compared to enasidenib-treated subjects were AST increased, dizziness, thrombocytopenia, and fall.

The incidence of Grade 3 nausea, increased blood bilirubin, decreased appetite, and IDH differentiation syndrome were also higher among enasidenib-treated subjects.

Less common with enasidenib as compared to gilteritinib were TEAEs suggestive of more severe myelosuppression, including Grade 3 febrile neutropenia (23.4% compared to 36%) and Grade 4 neutropenia and platelet count decreased (4.2% for both TEAEs with enasidenib compared to 7% and 12% with gilteritinib).

Comparison to Chemotherapy: Enasidenib versus Cytarabine in the CLASSIC I and VALOR Trials in Relapsed or Refractory Acute Myeloid Leukemia

The comparison of the baseline characteristics are presented in table OVsaf16

Table OVsaf16: Baseline Demographic and Disease Characteristics for Enasidenib-treated and Ara-C-treated Subjects

Parameter	Enasidenib R/R AML 100 mg Dose (n=214)	CLASSIC I Ara-C (n=158)	VALOR Ara-C (N=355)
Age, Median (Minimum, Maximum) (years)	68.0 (19, 100)	67 (55, 86)	63 (18-82)
Male, n (%)	109 (50.9)	101 (63.9)	192 (54)
Cytogenetic risk[a], n (%)			
Favorable	0	9 (5.7)	9 (4)
Intermediate	108 (50.5)	84 (53.2)	155 (65)
Adverse[b]	62 (29.0)	61 (38.6)	75 (31)
Lines of previous treatment for AML[c], n (%)			
1	101 (47.2)	100	100
2	65 (30.4)	0	0
≥ 3	48 (22.4)	0	0
ECOG, n (%)			
0	49 (22.9)	48 (30.4)	143 (41)
1	132 (61.7)	92 (58.2)	162 (46)
2	32 (15.0)	18 (11.4)	48 (14)

Ara-C = placebo + cytarabine, ECOG = Eastern Cooperative Oncology Group, n = number, NR = not reported, R/R = relapsed or refractory acute myeloid leukemia.

[a] Data are not available for some subjects.

[b] Enasidenib data are reported as "Poor risk" and "Failure" categories in Study AG221-C-001.

[c] Enasidenib data are reported as 3, 4, and ≥5 lines of treatment categories in Study AG221-C-001.

Data as of the 01 Sep 2017 cutoff for Study AG221-C-001 and based on the safety analysis set, and as reported by Faderl et al and Ravandi et al, based on the efficacy analysis set and the enrolled population, respectively.

Source: Table 14.1.7.7 of AG221-C-001, Table 14.1.6.7 of AG221-C-001, Table 1 of Faderl, 2012, and Table 1 of Ravandi, 2015.

Grade 3 TEAEs that occurred with higher incidence (approximately two times higher) among enasidenib-treated subjects than the VALOR study Ara-C-treated subjects were pneumonia (10.3% compared to 5%), fatigue (6.5% compared to 2%), dyspnea (6.1% compared to 2%), nausea (4.2% compared to 1%), and neutropenia (2.8% compared to 1%).

Grade 3 TEAEs that occurred with higher incidence (approximately two times higher) among enasidenib-treated subjects compared to the CLASSIC I study in Ara-C-treated subjects were anemia (22.0% compared to 8%), blood bilirubin increased (5.6% compared to 1%), and neutropenia, hyponatremia, and hypotension (each 2.8% compared to 1%).

Post marketing experience

On 01 Aug 2017, enasidenib was approved in the US under the trade name of Idhifa for the treatment of adult patients with R/R AML with an IDH2 mutation (as detected by an FDA approved test) at a dose of 100 mg daily until disease progression or unacceptable toxicity. Enasidenib has not been approved for use in any other country. It is estimated that 250 patients were treated with commercial Idhifa as of 01 Dec 2017, based on drug distribution data.

Table OVsaf17 presents the Post-marketing Serious Adverse Events Reported in More than One Patient:

Table OVsaf17: Post-marketing Serious Adverse Events Reported in More than One Patient

Primary SOC	Preferred Term	Patients with SAEs Post-marketing	Total SAEs[a]	Related SAEs[a]
Total Reported		**61**	**94**	**88**
Blood and lymphatic disorders	Neutropenia	2	2	2
	Pancytopenia	2	2	2
Gastrointestinal disorders	Nausea	2	2	2
General disorders and administration site conditions	Death	21	21	20
	Pyrexia	3	3	3
Investigations	Blood potassium decreased	2	2	2
	Full blood count decreased	2	2	2
	Platelet count decreased	7	7	7
	Red blood cell count decreased	2	2	2
Metabolism and nutrition disorders	Tumour lysis syndrome	3	3	3
Musculoskeletal and connective tissue disorders	Back pain	2	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	8	8	4
Respiratory, thoracic and mediastinal disorders	Acute promyelocytic leukaemia differentiation syndrome	2	2	2

AML = acute myelogenous leukemia, incl = including; R/R = relapsed or refractory, SAE = serious adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

[a] Number of SAEs that were reported more than once.

Coded using MedDRA dictionary v20.1.
Data as of the 01 Dec 2017.
Source: Celgene Drug Safety database (data on file).

A total of 26 deaths were reported for patients treated with Enasidenib. The causes of death, as recorded in the Celgene Drug Safety database, were death, AML, and respiratory disorder.

Primary SOC	Preferred Term	Patients with SAEs Post-marketing	Total SAEs[a]	Related SAEs[a]
Total Reported		**61**	**94**	**88**
Blood and lymphatic disorders	Neutropenia	2	2	2
	Pancytopenia	2	2	2
Gastrointestinal disorders	Nausea	2	2	2
General disorders and administration site conditions	Death	21	21	20
	Pyrexia	3	3	3
Investigations	Blood potassium decreased	2	2	2
	Full blood count decreased	2	2	2
	Platelet count decreased	7	7	7
	Red blood cell count decreased	2	2	2
Metabolism and nutrition disorders	Tumour lysis syndrome	3	3	3
Musculoskeletal and connective tissue disorders	Back pain	2	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	8	8	4
Respiratory, thoracic and mediastinal disorders	Acute promyelocytic leukaemia differentiation syndrome	2	2	2

AML = acute myelogenous leukemia, incl = including; R/R = relapsed or refractory, SAE = serious adverse event, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

[a] Number of SAEs that were reported more than once.

Coded using MedDRA dictionary v20.1.
Data as of the 01 Dec 2017.
Source: Celgene Drug Safety database (data on file).

A total of 26 deaths were reported for patients treated with Enasidenib. The causes of death, as recorded in the Celgene Drug Safety database, were death, AML, and respiratory disorder.

3.3.9. Discussion on clinical safety

The assessment of the safety profile of oral enasidenib as single agent the claimed indication (e.g. for the treatment of adult patients with r/r AML with an IDH2 mutation) is mainly based on data from *pivotal study AG221-C-001*, a phase 1/2 multicenter, open-label, dose escalation and expansion trial in subjects with advanced hematologic malignancies and an IDH2 mutation. The data cut-off date for the provided safety analyses was September 1, 2017. The available safety data were presented pooling data from the Phase 1 and Phase 2 parts of the pivotal study, according to 3 different cohorts: 1) subjects with R/R AML treated with recommended dose of 100 mg daily (n=214); 2) all subjects with R/R AML treated at any dose (n=280); 3) all subjects treated at any dose, irrespective to the diagnosis (n=345).

Additional safety data came from sponsored ongoing studies in subjects with hematologic malignancies (AG-221-AML-004, AG-221-AML-005, AG120-221-C-001), an Investigator initiated trial (BAML-16-001-S3), completed studies in healthy subjects (AG221-C-002, AG-221-CP-001, and AG-221-CP-002) and one completed study in subjects with solid tumours (AG221-C-003). Overall, 688 adults were exposed to enasidenib (healthy subjects: n=106; any AML: n=535; R/R AML: n=396; MDS and others malignancies: n=47). Further safety information regarding the use of enasidenib outside from clinical trials came from the compassionate use program and post-marketing reports in the US.

Clinical safety data was collected to include standard reporting of AEs, SAEs, vital signs, ECGs and other laboratory data. Additional safety assessments were done by organ system or syndrome and included evaluation of enasidenib related differentiation syndrome (IDH differentiation syndrome), non-infectious leukocytosis, tumour lysis syndrome, gastrointestinal disorders, hyperbilirubinemia and hepatic safety, renal safety, cardiac safety, blood and lymphatic system disorders, and infections.

Across the *Safety Analysis Set* (SAS) of 345 patients from study AG221-C-001, the majority were male (58.3%) and white (77.4%). Median age was of 69 years with the majority of patients (67%) aged 65 years or older and with an ECOG score ≥1 (76.8%). Similar demographic features were observed in the other ongoing studies, with the exception of a lower median age in studies AG120-221-C-001 and AG221-C-003 studies (61 and 62 years, respectively). Overall, in light of the rare claimed indication, the *size of the safety database* is considered adequate, and the observed demographic and disease-related features in the SAS are overall representative of the target population. In particular, the majority of subjects in the SAS (280/345) had R/R AML as per the claimed indication.

As a general concern, it should be noted, however, that the uncontrolled design of pivotal study AG221-C-001 limits robust evaluation of enasidenib safety profile, in particular when the known heterogeneity of AML in terms of disease symptoms, organ involvement and toxicity from prior regimens is taken into account. To overcome these limitations, the Applicant also submitted the results from an indirect comparison exercise evaluating safety data from pivotal study AG221-C-001 vs. data from 3 studies that were selected based on similar AE reporting requirements. However, significant differences in terms of patient-, disease-related characteristics and treatment exposure were observed across trials, and the methods used to adjust for such differences (e.g. limiting the analysis to TEAEs from pivotal study AG221-C-001 with onset through Cycle 3) is not considered adequate to capture the full toxicity profile of enasidenib. Most importantly, similar inclusion/exclusion criteria are not sufficient to account for all the possible variables with a potential significant impact on safety in such a heterogeneous setting. Only data from proper randomization in the context of well-controlled trials are therefore considered adequate to inform B/R evaluations in a regulatory context.

The chosen dose regimen for enasidenib was 100mg QD on days 1 to 28 in 28-days' cycles. The median time of *exposure* to enasidenib in the SAS was 4.2 months (7.3 cycles) for the overall population and 4.6 months for patients with R/R AML treated with 100 mg. Only 55 patients (15.9%) received more than 12 cycles. Although short, the reported median exposure can be considered acceptable in light of the high-risk population evaluated in the pivotal study, yet further characterization of the long-term toxicity profile of enasidenib is still considered of interest. Most of subjects with R/R AML who received enasidenib at the target dose for MA discontinued treatment (203/214; 94.9%) mainly due to disease progression (12.3%), while AEs were the second main reason for discontinuation (11.3%).A total of 344 (99.7%) subjects experienced at least 1 and 284 (82.3%) subjects experienced at least 1 TEAE that was suspected by the investigator to be related to enasidenib. Overall, 307 (89.0%) subjects had a TEAE that was Grade 3 or 4 in severity, 151 (43.8%) subjects had a treatment-related TEAE that was Grade 3 or 4 in severity. 277 (80.3%) subjects had a TESAE, 92 (26.7%) subjects had a treatment related TESAE. 65 (18.8%) subjects had a TEAE leading to enasidenib discontinuation, 16 (4.6%) had a treatment related TEAE leading to discontinuation.

There were 121 (35.1%) on-treatment all-cause deaths. Most of these events of death were caused by disease progression or TEAEs related to the underlying malignancies.

The proportion of subjects who experienced a TEAE, treatment-related TEAE, Grade 3 or 4 TEAE, or TESAE was similar in subjects with R/R AML versus the entire population of subjects with hematologic malignancies enrolled in this study. However, it is notable that the study population is very heterogeneous. Factors such as age at relapse, relapsed or refractory disease, nature of AML (de novo vs secondary), cytogenetics, relapse-free interval from first CR, number of prior therapies, prior HSCT,

the performance status of the patients (list incomplete) all may affect to different degrees the presented safety data. In addition, it should be kept in mind that the targeted population based on the claimed indication is significantly broader than the studied population, including also lower-risk R/R AML patients and R/R AML patients in the curative setting.

Besides elevation of blood bilirubin, no dose-dependent trends across the dose groups were noted for any of the subcategories of TEAEs and incidences and type of TEAEs were similar.

The potential ADRs were adequately presented by the applicant. However, they are still not entirely properly reflected in the SmPC (see LoQ).

The TEAEs of enasidenib related differentiation syndrome, leucocytosis and tumour lysis syndrome as well as gastrointestinal disorders and hyperbilirubimemia were determined as ADRs associated with the mechanism of action of enasidenib.

IDH Differentiation syndrome is a life-threatening drug related adverse event comparable with the "retinoid acid syndrome" (differentiation syndrome) described for retinoid acid (e.g. for Vesanoid) in treatment of acute promyelocytic leukemia (APL). It is characterized by rapid weight gain, pleural and pericardial effusions, peripheral oedema, respiratory distress, and fever. The actual incidence of IDH DS is hard to establish, due to frequent overlapping with other clinical manifestations, such as e.g. respiratory failure consequent to infections. In the Phase 1/2 study treatment-emergent AEs of "IDH differentiation syndrome" were reported in 39 (11.3%) subjects and, with the exception of 1 case, all were attributed to the study drug treatment. Treatment emergent events Grade 3 were reported in 22 (6.4%) patients. In addition, IDH differentiation syndrome was considered a TESAE for 25 (7.2%) subjects. The first episode occurred mostly within the first 3 months on treatment and it can be accompanied by leucocytosis and TLS. No significant impact of baseline patient and disease characteristics on the chance to develop IDH DS were observed, with the exception of a possible trend towards a higher risk for subjects with >30% bone marrow blasts at baseline. However, to better understand and assess the enasidenib-related differentiation syndrome more precisely, further data /analysis have to be provided. The Applicant stated to complete a meta-analysis to characterize enasidenib-related differentiation syndrome, specifically incidence, appropriate diagnostic criteria, and effective treatment based on patient-level data and pooled analyses for on-going trials in patients with acute myeloid leukaemia: AG221-C-001, AG-120-221-C-001, AG-221-AML-004, and AG-221-AML-005 as a post-approval commitment.

While WBC elevation is commonly caused by infectious processes and is frequent in patients with hematologic malignancies, leucocytosis not associated with infectious processes or disease progression has been observed with enasidenib. The cause of enasidenib-associated *non - infectious leukocytosis* is likely to be similar to that of IDH differentiation syndrome, but it does not involve WBC migration from the intra-vascular space. In the Phase 1/2 study, treatment-emergent AEs of leukocytosis (all grades) were reported in 53 (15.4%) subjects. 4.6% of TEAs were considered treatment related. Treatment-emergent AEs Grade 3-4 were reported in 19 (5.5%) subjects. 1.7% of TEAs were considered treatment related. Non-infectious leukocytosis was considered a TESAE for 22 (6.4%) subjects; for 8 (2.3%) subjects, the TESAE of non-infectious leukocytosis was considered related to study treatment. In the absence of a proper control, however, reliable estimates on the actual incidence of enasidenib-related vs. leukaemia-related NIL are difficult. The incidence on NIL seems to be dose-related, with the highest frequency observed in subjects who received >100 mg of enasidenib. Overall, based on the available data, when unrelated to disease progression, NIL does not appear to be life-threatening, and seems to be manageable with the start of hydroxyurea.

Tumour lysis syndrome is known to occur spontaneously in patients with hematologic malignancies and can also be associated with hydroxyurea use. Detailed review of the cases by the Sponsor indicated that

a portion of the cases of tumor lysis syndrome followed the onset of IDH differentiation syndrome and were likely caused by breakdown of WBC infiltrates in the peripheral tissue. Overall, 27 (7.8%) subjects had a TEAE (all grades) of tumor lysis syndrome. Thirteen (3.8%) subjects had tumor lysis syndrome that was considered by the investigator to be treatment related. Treatment-emergent AEs Grade 3-4 were reported in 19 (5.5%) subjects. 1.7% of TEAs was considered to be treatment related. Tumor lysis syndrome was considered a TESAE for 21 (6.1%) subjects. The rationale behind the relationship between TLS and DS with enasidenib is understood, yet it should be considered that most of the reported cases of TLS were difficult to diagnose due to the frequent overlapping with other adverse events (e.g. IDH DS, disease progression and other causes of hyperuricaemia) and the lack of proper controls.

Treatment-emergent AEs in the SOC *gastrointestinal disorder* were reported for 88.1% of subjects overall, and approximately half of the events (43.8%) were considered by the investigator to be treatment related. Gastrointestinal disorder TESAEs were reported for 22.3% of subjects. Most AEs were easily managed and did not represent a severe or life-threatening condition. On the other hand, however, the impact of GI complications on QoL in the context of chronic treatments is known, and no comprehensive evaluation of patient-reported outcomes from uncontrolled study AG221-C-001 was available. Reassuringly, treatment interruptions and dose modifications due to GI TEAEs were uncommon.

Overall, 104 (30.1%) subjects had at least one TEA from the SMQ *acute renal failure*. Generally, these events were associated with drug-related IDH differentiation syndrome, tumour lysis syndrome, or dehydration caused by gastrointestinal disturbances, or were otherwise associated with AML complications, such as severe infections; the events were transient and fully reversible, not resulting in sustained kidney damage. Preliminary data from controlled studies AG221-AML-004 and AG221-AML-005 consistently show that no clear direct causal relationship between exposure to enasidenib and renal damage can be established. Overall, the available clinical data suggest that the potential for direct renal damage with enasidenib is low.

TEAEs associated with *bilirubin elevation* were very common and dose-dependent increases were observed for total and indirect bilirubin and, to a lesser degree, for direct bilirubin.

In summary, *blood bilirubin increased* was reported in 117 (33.9%) subjects, hyperbilirubinemia in 31 (9.0%) subjects, jaundice in 5 (1.4%) subjects, and bilirubin conjugated increased in 3 (0.9%) subjects. Most of these TEAEs within the biliary SMQ were assessed as related to study drug by the investigators (86.3%; 120/139). Treatment-emergent AEs Grade 3-4 were reported in 49 (14.2%) subjects. 10.4% of these TEAs were considered to be treatment related. The TESAEs within the SMQ Biliary System Related Investigations, Signs and Symptoms, were reported for 8 (2.3%) subjects; most of these subjects (75.0%; 6/8) had events that were assessed as related to study drug by the investigators.

Fifteen subjects in study AG221-C001 developed elevated ALT or AST (at least 3x above the ULN) with concomitant increased serum total bilirubin levels (> 2× the ULN). Most AEs of elevated liver enzymes observed during treatment with enasidenib occurred, however, in the context of systemic complications (e.g. leukocytosis, IDH DS, infections) or during concomitant exposure to other drugs with hepatotoxic potential (e.g. acetaminophen). Further, in the vast majority of cases, AST/ALT returned to normal levels without enasidenib interruption/discontinuation. Conversely, total bilirubin levels usually remained above the ULN, as expected during treatment with enasidenib.

Overall, the available data suggest that it is unlikely that enasidenib has a significant potential for direct liver injury. On the other hand, the absence of data from randomized controlled trials does not allow to clearly disentangle the actual contribution of enasidenib and that of the underlying disease and/or concomitant conditions/medications to the observed hepatic toxicity.

A significantly higher number of grade ≥3 TEAE was observed in subjects with UGT1A1 allele mutation vs wild type. However, most AEs were managed with temporally drug interruption or dose reduction and did not seem to be associated with increased rates of liver injury; based on the available data, no restriction of starting dose was recommended in patients with UGT1A1 gene mutation.

There seems to be a dose-dependent *QTc prolonging potential* of enasidenib. 11.2% (24/214) of subjects with r/r AML who received enasidenib 100mg experienced at least one SMQ TEAE (6.4% a TEAE of QT prolongation). However, this assessment is limited by the uncontrolled design of the current study and multiple potential confounders (e.g. concomitant use of drugs with a known QT-prolonging effect, concurrent electrolytes abnormalities etc.). Overall, based on the available data, the potential for QTc prolongation of enasidenib seems limited and reduced compared to the IDH1 inhibitor ivosidenib. Consequently, the current information provided in section 5.1 of the SmPC (Pharmacodynamic effects) can be considered adequate. The inclusion of QT interval prolongation resp. Torsades de points as an important potential risk in the RMP is endorsed, and further investigation in the ongoing Phase III trials is expected.

Treatment with enasidenib seems to reduce TEAEs in the SOC of *blood and lymphatic system disorders* over time, at least in patients that respond to treatment. These findings are not surprising as haematologic improvements in platelets, haemoglobin and ANC, such as those associated with response to enasidenib or other AML therapeutics, are generally accompanied by a reduction in adverse events associated with these laboratory parameters; i.e. bleeding events, infections and febrile neutropenia. However, the magnitude of these effects cannot be contextualized, as study AG221-C-001 is uncontrolled.

Of note, *lab values of platelets* counts indicate a moderate drop in the first 3 therapy cycles indicating potential for increased risk of thrombocytopenia.The uncontrolled design limits a robust evaluation of enasidenib safety profile regarding myelosuppression, in particular when the known heterogenecity of AML in terms of disease symptoms, organ involvement and toxicity from prior regimens is taken into account. However, with regard to the presented data in the dossier as well in the literature (Stein 2017 Blood) a myelosuppressive effect cannot be entirely excluded. Thus, the applicant should consider to add at least Thromboytopenia (and Anemia) to section 4.8 of the SmPC (see LoQ)

Infective TEAEs were also commonly observed with enasidenib (73.8%): mainly sepsis (15.4%) and pneumonia (21.7%), often associated with febrile neutropenia (36.9%). The incidence of grade 3-4 infections in pivotal trial AG221-C-001 study (50%) is not considered significantly different from that reported with common chemotherapy salvage regimens in R/R AML, and this is unexpected due to the pro-differentiating mechanism of action of enasidenib. In summary, being R/R AML patients intrinsically at risk of infections, a causal link between enasidenib exposure and infection occurrence is hardly assessable in a single uncontrolled trial, although possible myelosuppressive effect of enasidenib cannot be definitively excluded, especially in the first treatment cycles, when the positive effects of re-established cell differentiation are not yet evident. The applicant is asked to provide more information regarding these issues. The Applicant highlighted the difficulties in performing indirect comparisons between enasidenib treatment and conventional chemotherapy in terms of infective risk. The limits of indirect comparisons are acknowledged, and it is agreed that definitive conclusions cannot be drawn. On the other hand, however, the limited available data are not considered sufficient to support reliable claims of reduced infective risk with enasidenib compared to standard alternatives in r/r AML. Safety data from direct comparison in the ongoing Phase III study are therefore needed to conclude on the actual infective risk with enasidenib.

In addition, the Applicant has analysed data on the antibacterials, antimycotics and antivirals used either as treatment or prophylaxis in study AG221-C-001 as requested. The limits of this post-hoc analysis are recognized. However, it can be concluded that currently there is no evidence that mandatory

antimicrobial prophylaxis could result in a reduced infective risk with enasidenib in the proposed indication. No changes in the proposed SmPC are proposed.

Twelve out of the 214 (5.6%) R/R AML patients treated with Enasidenib 100 mg experienced a *peripheral sensory neuropathy (PN)* that was considered treatment-related by investigators.

However, it is recognized that the available data from study AG221-C-001 are not sufficient to unambiguously confirm the casual relationship between enasidenib and the observed PN events, in particular since, in most cases, alternative causes of PN could be identified. Reassuringly, preliminary safety data from phase III studies AG221-AML-004 and AG221-AML-005 also do not show an increased risk of PN with enasidenib compared to azacitidine, LDAC or IDAC.

From a nonclinical perspective, the conducted animal/in vitro studies cannot be considered an adequate model for evaluating the risk of PN in humans, yet it can be agreed that the data did not show that the mechanism of action of enasidenib was related to an increased risk of PN.

Regarding further *laboratory findings,* increases in mean uric acid and mean serum creatinine reflecting tumor lysis syndrome as well as increase of mean total bilirubin (with corresponding increase in BUN) were reported as common resp. very common biochemistry abnormalities. However, these abnormalities are mainly due to the mode of action of enasidenib.

The safety profile of enasidenib seems to be consistent across the considered *age classes*, although the reduced sample size does not allow for robust evaluations in the very elderly subset. The limited information in subjects aged 85 is reflected in the SmPC as requested.

The supportive study AG221-C-003 included subjects with advanced solid tumours, including glioma, and subjects with angioimmunoblastic T-cell lymphoma, that harbour an IDH2 mutation. The ADRs of enasidenib were consistent with those in the hematologic malignancy study, except that, as could be expected in non-blood tumours, no events of IDH differentiation syndrome or non-infectious leukocytosis were observed in this study.

Due to the small numbers of enrolled subjects, safety data of the supportive studies (AG120-221-C-001, AG-221-AML-004, and AG-221-AML-005) have not been analysed. In addition – due to the singular application of enasidenib in the studies with healthy subjects (AG221-C-002, AG-221-CP-001, and AG-221-CP-002) no clinically significant adverse events attributable to enasidenib were observed.

The safety data provided from the post marketing experience was comparable with the data reported in the clinical trial settings.

The provided review of all fatal events observed outside clinical trials did not highlight unexpected safety concerns, although the high rate of missing information limits the reliability of the data. However, this issue still needs to be adequately addressed in the SmPC (see LoQ). The Applicant's concerns with respect to the negative impact of delayed treatment for DS observed when non-haematologist health care professionals have been involved in patient management is shared, and the proposed risk-minimization measures (i.e. Wallet Card and Healthcare Educational Materials) are considered acceptable.

In summary, the applicant studied and discussed the safety profile of enasidenib monotherapy mainly with regard to the safety data analysed for Study AG221-C-001. Overall, the described toxicities appear to be manageable. However, as Study AG221-C-001 was a single-arm study without an active comparator arm not all issues could be completely elaborated and should further be pursued in study AG221-C-004.

3.3.10. Conclusions on clinical safety

Overall, the available data suggest that the safety profile of enasidenib is not negligible (potential life-threatening AEs like IDH DS were identified). However, the evaluation of the safety profile is hampered due to the uncontrolled nature of the study data, the heterogeneity of the underlying conditions of the patients to be treated and/or the use of concomitant medicinal products (e.g. antifugal/antibiotics). Interpretation of the safety profile of enasidenib in the context of literature data is difficult and inconclusive at the end.

Key safety concerns identified were elevation of blood bilirubin, enasidenib related (IDH) differentiation syndrome, non-infectious leucocytosis, tumour lysis syndrome, gastrointestinal disturbances.

In summary, the safety profile appears to be manageable.

Safety data regarding hepatic impairment and as drug-drug interactions as well as long-term safety data is currently incomplete respectively missing and thus cannot be assessed entirely.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 3.4.1: Summary of the Safety Concerns **as proposed by the applicant**

Summary of safety concerns	
Important identified risks	Differentiation syndrome Tumour lysis syndrome
Important potential risks	Foetal toxicity Torsades de pointes
Missing information	Safety in patients with moderate to severe hepatic impairment Safety in elderly patients (≥ 85 years of age) Long-term safety

Discussion on safety specification

The safety specification presented in the RMP is largely acceptable. However, certain modules require revision and/or additional data is needed for a final conclusion.

- Update safety concerns as follows:
    - Please update the missing information "Safety in elderly patients (≥ 85 years of age)" to "Safety in elderly patients (≥75 years of age)"

– The MAH is reminded that safety concerns of RMP and PSURs may differ. For enasidenib PSURs only TLS and non-infectious leucocytosis are considered important identified risks. In addition, phototoxicity should be closely monitored in PSURs and detailed information should be provided.

Conclusions on the safety specification

The CHMP Rapporteur considers that the following issues should be addressed:

The Rapporteur considers that the following should also be safety concerns:

Missing information

– Safety in Elderly patients (≥ 75 years of age) (instead of an age threshold of 85 years of age)

Table 5.2.2: Summary of the Safety Concerns **as proposed by the CHMP Rapporteur**.

Summary of safety concerns	
Important identified risks	Differentiation syndrome Tumour lysis syndrome
Important potential risks	Foetal toxicity Torsades de pointes
Missing information	Safety in patients with moderate to severe hepatic impairment Safety in Elderly patients (≥ 75 years of age) Long-term safety

3.4.2. Pharmacovigilance Plan

Routine pharmacovigilance activities

Apart from reporting of adverse drug reactions and signal detection activities, the Applicant included, as routine pharmacovigilance activities, four specific adverse reaction follow-up questionnaires to further characterise the following safety concerns:

- Differentiation Syndrome
- Tumour Lysis Syndrome
- Torsades de pointes
- Pregnancy (foetal toxicity)

These questionnaires are presented in Annex 4 of the RMP and are acknowledged.

Summary of additional PhV activities

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
AG-221-AML-004[a]	To investigate whether the effect of enasidenib on response translates into survival prolongation in R/R AML patients ≥ 60 years old with an IDH2 mutation.	Long-term safety Safety in elderly patients.	Estimated study completion: Q3 2022.	
Category 3 - Required additional pharmacovigilance activities				
Meta-analysis to characterise IDH differentiation syndrome (Studies AG221-C-001, AG 221-AML-004, AG 221-AML-005 and AG120 221 C 001)	To characterise IDH differentiation syndrome, specifically incidence, appropriate diagnostic criteria, and effective treatment based on patient level data and pooled analyses for ongoing trials in patients with AML.	Differentiation syndrome. Long-term safety.		
CC-90007-CP-003	To assess the PK of enasidenib in patients with moderate and severe hepatic impairment.	Safety in patients with moderate to severe hepatic impairment.		

[a] If Study AG-221-AML-004 becomes a mandatory or imposed PAES by CHMP, this information will be moved and reflected under the PAES section.

From version 0.2 to version 0.3 of the RMP, the Pharmacovigilance Plan was updated with the removal of Category 3 Study CC-90007-CP-004, to address "Drug-drug interactions". This removal was related with the fact that DDI is not considered as a safety concern therefore the Applicant removed it.

The category 2 study AG-221-AML-004 is mainly design as a confirmatory trial on the efficacy of Idhifa and designed with the following rational: To investigate whether the effect of enasidenib on response translates into survival prolongation in R/R AML patients ≥ 60 years old with an IDH2 mutation; and with the following objectives: Primary objective: to determine the primary efficacy, measured as overall survival, of enasidenib compared with CCRs; Secondary objectives: To determine the supporting efficacy of enasidenib compared with CCRs; To determine the safety and tolerability of enasidenib compared with CCRs; To determine the effect of enasidenib compared with CCRs on health-related quality of life. Considering the definition of a PASS included in the GVP Module VIII, this Study as proposed by the applicant does not qualify as a PASS and therefore it should be removed from Part III of the RMP. (OC)

The table of "On-going and planned additional pharmacovigilance activities" should include the status of the studies, therefore the applicant is requested to complete the table as requested. (OC)

The applicant was requested in the previous round of assessment to consider the conduction of a study to evaluate the effectiveness of the additional risk minimisation measures, and to update the Pharmacovigilance Plan accordingly. No such update was made although the applicant responded that they will consider the conduction of a study. We remind the applicant that the Pharmacovigilance plan

must be totally agreed before the granting of the marketing authorisation, therefore a satisfactory proposal with the objective of measuring the effectiveness of the risk minimisations measures, whether it is in a PASS format or any other proposal with a proper justification must be provided. (OC)

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product and the applicant should propose PhV studies.

The PRAC Rapporteur also considered that the Applicant should propose a study to monitor the effectiveness of the prescriber's educational material on DS.

3.4.3. Plans for post-authorisation efficacy studies

From the previous round of assessment, the Applicant was advised that study AG-221-AML-004, could not continue to be considered both as PASS and PAES. Then, the Applicant chose to maintain it as a PASS and committed to switch it to Part IV as a PAES in case a conditional approval was granted. At this point, the maintenance of this study as a PASS is being questioned, as the study is not primarily designed to address safety aspects.

Therefore, the inclusion of study AG-221-AML-004 as a PAES in this section is pending on the Rapporteur's decision on the approval of a conditional MA.

3.4.4. Risk minimisation measures

Summary of additional risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Differentiation Syndrome	SmPC and PL, IDH-differentiation syndrome publications **Routine risk minimisation measures:** Differentiation syndrome is listed as a serious adverse reaction in Section 4.8 of the SmPC and signs and symptoms are included in Section 4.4 of the SmPC. Differentiation syndrome is listed as a serious side effect in the PL. Recommendations for management of differentiation syndrome including treatment, dose modification, monitoring and recommended actions are presented in Sections 4.2 and 4.4 of the SmPC.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for adverse reactions. **Additional pharmacovigilance activities:** Meta-analysis to characterise IDH differentiation syndrome.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Healthcare professional information. Patient alert card.	
TLS	SmPC and PL **Routine risk minimisation measures:** TLS is listed as a serious adverse reaction in Section 4.8 of the SmPC and as a serious side effect in the PL. Recommendations for dose modification or interruption and monitoring of blood counts and blood chemistries are provided in Section 4.2 of the SmPC. Signs and symptoms and advice on symptom management is provided in Section 4.4 of the SmPC. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up questionnaire for adverse reactions. **Additional pharmacovigilance activities:** None proposed
Foetal Toxicity	SmPC and PL **Routine risk minimisation measures:** Warnings and advice to the patient regarding the potential risk to a foetus and that enasidenib may affect the efficacy of systemic hormonal contraceptives are included in Sections 4.4 and 4.6 of the SmPC. Preclinical reproductive and developmental toxicity findings are included in Section 5.3 of the SmPC. Warnings and advice are included in the PL. Recommendation for women of childbearing potential to have a pregnancy test prior to starting treatment with enasidenib and advice regarding the use of highly effective contraception are included in Sections 4.4 and 4.6 of the SmPC.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy follow-up questionnaire. **Additional pharmacovigilance activities:** None proposed.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None proposed.	
Torsades de Pointes	SmPC **Routine risk minimisation measures:** Dose modifications and recommended actions for Grade 3 or higher toxicities considered related to treatment are included in Section 4.2 of the SmPC. **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** QT interval prolongation follow-up questionnaire. **Additional pharmacovigilance activities:** None proposed.
Safety in Patients with Moderate to Severe Hepatic Impairment	SmPC **Routine risk minimisation measures:** Enasidenib has not been formally studied in patients with moderately or severely impaired hepatic function and no specific dose recommendations can be made (Sections 4.2 and 5.2 of the SmPC). **Additional risk minimisation measures:** None proposed.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study CC-90007-CP-003.
Safety in Elderly Patients (≥ 85 Years of Age)	SmPC **Routine risk minimisation measures:** No overall differences in efficacy or safety were observed between patients aged 75 years or older, aged 65 years or older or younger patients. Population PK identified no apparent relationship between age and enasidenib exposure (Sections 5.1 and 5.2 of the SmPC). No dose adjustment is required for enasidenib based on age (Section 4.2 of the SmPC).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** Study AG-221-AML-004.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None proposed.	
Long-term Safety	SmPC **Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** 3 years safety follow-up from Study AG 221-AML-004 and Study AG221-C-001.

The applicant developed additional risk minimisation measures to address the risk of "Differentiation syndrome" in the form of a "Healthcare Professional information" document and a "Patient Alert Card"

The proposed key messages for these educational materials, as included in Annex 6 of the RMP, are as follows:

Healthcare Professional Information (Passport Size)

Healthcare Professional Educational information shall contain the following elements:

- Description of the signs and symptoms of differentiation syndrome.
- Management of differentiation syndrome.
- Importance of informing patients on the risk of differentiation syndrome and on the need to promptly seek medical attention in case they suspect differentiation syndrome.
- Importance of the inclusion of the prescriber's contact information in the Patient Alert Card.

Patient Alert Card (PAC)

The Patient Alert Card shall contain the following elements:

- Description of the risk of differentiation syndrome.
- Instructions on seeking medical care if differentiation syndrome is suspected.
- Fields that contain contact details of the prescriber, hospital, and department.

Although the mock-up of the PAC presented in Annex IIIA of the PI has information directed to any HCP that may assist the patien, this information was not included as a key message in Annex 6 of the RMP, and therefore it should be updated with the following: (OC)

- brief information on the risk of DS directed to other HCPs that can assist them in case of urgency.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.5. Summary of the risk management plan

The public summary of the RMP may require revision.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.3 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance system

The applicant has provided a Summary of the Pharmacovigilance System. A statement signed by the applicant and the qualified person for pharmacovigilance indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

In the last submitted summary of the applicant's pharmacovigilance system, Milan had been announced as the future QPPV site and PSMF location after 29 March 2019. In the latest documentation submitted in July, no new summary with a new QPPV site and PSMF location was submitted. As the change in QPPV site and PSMF location has already become effective in Art. 57, a new summary should be available.
The Rapporteur requests the submission of an updated summary of the applicant's pharmacovigilance system with the current QPPV site and PSMF location.

Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, this is considered acceptable by the CHMP.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Orphan medicinal products

Orphan designation
On 28 April 2016, orphan designation (EU/3/16/1640) was granted by the European Commission to the Applicant, for 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4 yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate for the treatment of acute myeloid

leukaemia. According to the conclusion of the COMP the prevalence of the "condition" 'treatment of acute myeloid leukaemia' is 1 per 10.000 individuals in the EU.

Similarity
The assessment of similarity is appended to this report.

Derogation(s) from market exclusivity
NA

5. SAG oncology consultation

The scientific advisory group (SAG) Oncology was consulted during this procedure with regard to the relevance of the enasidenib data to support an indication in R/R AML with an IDH2 mutation

Final minutes and answers from the Scientific Advisory Group in Oncology meeting on Idhifa (enasidenib)

CHMP questions with SAG responses

As a general comment the SAG agreed with the scientific evaluation that the benefit-risk assessment is difficult due to the non-randomized design of the pivotal study.

Although in advanced haematological malignancies in patients with no good alternatives it is often possible to identify some clinical benefits from single-arm studies, like symptom control for a sufficient duration, the description of benefits and risks is fraught with many uncertainties about important time-related endpoints, quality of life, and toxicity. External controls rarely lead to convincing conclusions about such endpoints especially when populations are heterogeneous in terms of outcomes, when prognostic factors are incompletely understood, and/or when data about important prognostic factors are unavailable. All of these deficiencies apply to the externally controlled analyses presented.

For such clinical development, mainly based on exploratory studies, maximising data collection from patients treated outside clinical trials would have been useful including data on response rate and duration, time to progression, subsequent therapies, and survival data including cause of death. Regrettably, these data were not available. To minimise some of the remaining uncertainties, such data should be carefully collected (using quality-assured methods and frequency of assessment for response evaluation as for confirmatory trials) and submitted post-approval.

Similarly, the lack of systematic information on co-mutations present at the time of inclusion (with proper multivariate analyses vs IDH2 and relevant clinical factors) plus the lack of comprehensive genomic work-up at time of progression are also key omissions that could easily have been avoided. If samples are available from the trials, appropriate analyses should be conducted retrospectively. Furthermore, such data should be collected systematically post-approval and submitted for evaluation together with data on clinical outcomes.

1. What is known about the prognostic impact of IDH2 mutations in the R/R AML setting?

The prognostic importance of IDH2 mutations in the setting of R/R AML is not well understood. AML is a highly heterogeneous disease with respect to morphology, immunophenotype, cytogenetics and molecular genetics, and clinical factors. Available meta-analyses of partially overlapping studies have shown inconsistent results.

In the clinical trial presented, which was enriched for IDH2 mutations, the overall survival duration was very poor although the prognostic effect cannot be distinguished from other correlated prognostic factors (e.g., duration of remission to induction treatment, age).

The prognostic importance is better understood in the frontline setting in patients treated with intensive CT. However, this effect cannot be assumed to apply as well to treatment of R/R AML.

2. Is the complete response rate and other outcomes seen in the AG221-C-001 indicative that treatment with enasidenib would provide clinically relevant efficacy in IDH2 mutated R/R AML patients?

There appears to be a mismatch between the claimed indication and the patients recruited (the study included many younger patients with few prior lines of treatment and good performance status for whom induction chemotherapy might have been an option).

First, an agreeable definition of relapsed/refractory should be defined as precisely as possible. This definition should include how the No. of courses and types of regimens are counted (e.g., how one regimen consolidation regimen with multiple agents is counted). Second, the applicant company should present a careful re-analysis of the subgroup of patients falling exactly within the scope of the claimed indication and present those data for the benefit-risk assessment.

Assuming that the results for the subgroup reflecting the claimed indication are similar to those presented in the current analyses, the SAG was in full agreement that convincing clinical efficacy has been established on the basis of the clinically significant proportion of patients that were transfusion-independent following treatment with the product. Transfusion-independence as defined in the study is considered to represent a clear benefit for some patients in view of the avoidance of possibly travel and hospital stay for the transfusion (even if some patients may still require access to hospital due to blood tests and visits). The benefit is still considered important even if patients still have to be followed by their treating physicians at regular intervals. The balance of benefits and risks of such treatment should be left to the clinical decision, taking into account benefits, harms, in the context of the available, non-standard, therapeutic options. The high response rate is also assumed to be associated with reduction in morbidities commonly associated with R/R AML. The safety profile is well described and seems acceptable.

No other favourable effects have been convincingly established.

Concerning overall survival, the external comparisons submitted are not convincing especially because important prognostic factors (e.g., duration of remission to induction treatment) were not taken into account. The responder-analyses presented are also unconvincing due to obvious biases such as "immortal time bias" that was not adequately taken into account

Concerning the ability for patients to proceed to transplantation, the indications for transplantation are too variable to allow to conclude a causal association with the product.

Health-related quality of life (HRQoL) data were not available to further characterise the benefits from the perspective of treated patients.

The data presented also lacked relevant measurements to explore important predictors of response. There is a need for a comprehensive investigation of factors associated with prognosis and, more importantly, outcome, using appropriate techniques (see below).

3. How do you evaluate the safety profile of enasidenib in the target population including the risk of IDH differentiation syndrome?

No important myelotoxicity was observed. The only possible concern is differentiation syndrome (which is expected) although this is manageable and similar to what is observed in treatment of APL (although for APL it is generally observed earlier versus up to 5 months after initiation of enasidenib). Adequate risk-minimisation measures (e.g., weekly blood samples in the induction phase and beyond for an appropriate duration) and educational material for health care professionals and patients about early symptoms (e.g., shortness of breath; fever; oliguria; weight gain) will be important to manage this risk.

4. In what ways might enasidenib provide an advantage compared to presently available therapies?

Currently, there is no salvage therapy for RR-AML that has shown a clinically relevant effect in terms of important clinical endpoints like OS or HRQoL. Hypomethylating agents are frequently used although the response rates are low and the overall survival is short. They are a reasonable therapeutic option for patients with RR-AML in the absence of clinical trials.

In view of the high rate of transfusion independence and the acceptable toxicity profile, the product can provide an advantage compared to available treatment options. No other effects have been convincingly established. There is a possibility that the high response rate and long duration of response is also associated with improvement in RFS, OS and HRQoL, at least in a subset of patients. However, this remains a hypothesis.

5. What further investigations, if any, are needed to characterise the efficacy and safety of enasidenib?

Before the benefits can be concluded in the claimed indication, the following are recommended:

- A re-analysis of the subgroup of patients falling exactly within the scope of the claimed indication as already discussed;
- Further details of prior therapies, namely proportion receiving intensive and non-intensive regimens and the exact nature of these regimens, plus the number of cycles of therapy and the number of regimens are required for each enasidenib-treated patient. An attempt should then be made to match the enasidenib trial population to the historical controls presented by the applicant.

Thereafter, to further refine the understanding of the benefits in the approved population, more comprehensive analyses (multivariate and longitudinal) using clinical characteristics and panel sequencing, including the role of IDH mutations and any co-mutations, to identify prognostic and predictive factors and investigating resistance mechanisms should be conducted. Ideally these should include exome or genome sequencing.

6. Benefit risk assessment

Enasidenib (AG-221, CC-90007) is an orally administered first-in-class, selective inhibitor of mutant IDH2 enzyme with activity against both R140 and R172 variants promoting the differentiation of leukemic cells into normalised mature cells.

6.1. Therapeutic Context

6.1.1. Disease or condition

The claimed therapeutic indication in this MAA for Idhifa (enasidenib) is:

- Initially proposed indication: "*Treatment of adult patients with relapsed or refractory acute myeloid leukaemia (R/R AML) with an isocitrate dehydrogenase 2 (IDH2) mutation*"
- Adapted to: *adult patients with intermediate or poor cytogenetic risk, relapsed or refractory AML with an isocitrate dehydrogenase 2 (IDH2) mutation who are ineligible for intensive treatment and*
    - *Have previously failed low intensity treatment, or*
    - *Have primary refractory disease or relapsed after having failed previous intensive treatment including haematopoetic stem cell transplantation.*

The Applicant recommends a dose of enasidenib of "100 mg to be taken orally once daily until disease progression or unacceptable toxicity". "Treatment for patients without disease progression or unacceptable toxicity is recommended for a minimum of 6 months to allow time for clinical response".

As to the study protocol (Amendment 7) of the pivotal phase 1/2 study AG221-C-001 the following definitions relevant for the therapeutic indication applied:

- ✓ Diagnosis of AML had to be performed according to WHO criteria (Swerdlow et al 2008).
- ✓ 'Relapsed' AML (defined only for subjects who have previously attained CR, CRi, CRp or MLFS) is defined as "bone marrow blasts ≥5 percent; or reappearance of blasts in the blood; or development of extramedullary disease)".
- ✓ 'Refractory' (resistant) AML is defined as "failure to achieve CR or CRi (general practice; Phase 2/3 trials), or failure to achieve CR, CRi or PR (Phase 1 trials); only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukaemia by blood and/or bone marrow examination".

Details of the definition of a positive IDH2 status which have been applied and which should be considered treatment relevant lack clarification (OC).

The frequency of reported IDH2 mutations in AML is between 8% and 19%. In subjects with IDH2 mutated AML, the R140 mutation is the more common and represents approximately 70% of the cases, while the R172 mutation represents approximately 30%.

Survival for R/R AML differs significantly due to the large heterogeneity of this target population; a literature review performed by the Applicant showed a median survival in the range of 2 to 13 months (CR in this review differed from 10.5% to 52%). The prognostic impact of mutated IDH2 in AML remains controversial. Currently it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH2 in AML.

While in the curative treatment setting of AML, OS and EFS are the most relevant efficacy endpoints, in the non-curative setting OS alone is considered the most relevant efficacy endpoint as the clinical relevance of CR (as one important aspect of the composite endpoint EFS) in patients not being able to

receive HSCT is not evident. These considerations apply to both 'newly diagnosed' and 'relapsed/refractory' AML.

6.1.2. Available therapies and unmet medical need

The overarching question to be decided in the treatment of both newly diagnosed AML and R/R AML is whether treatment intention is still curative. The only curative treatment option in AML is HSCT (mostly after intensive chemotherapy). However, intensive chemotherapy and HSCT are associated with a significant treatment-related morbidity and mortality and a long duration of hospitalisation. Therefore, the most important trade-off in every patient is to weigh the higher treatment-related morbidity and mortality and the long duration of hospitalisation being associated with intensive chemotherapy and HSCT against the possibility to be cured.

In R/R AML several intensive chemotherapy treatment options are commonly used, including intensive re-induction (with an anthracycline, anthracenedione and/or cytarabine) or purine analogue-containing (e.g. fludarabine, cladribine, clofarabine) salvage chemotherapy; but there is no intensive treatment regimen that is clearly more beneficial than another. Non-curative treatment options include hypomethylating agents (HMA), low-dose cytarabine (LDAC) and supportive care. In consequence, treatment in the R/R AML setting should be individualized and will depend on whether treatment with a curative intent is realistically possible and whether the patient can tolerate or wishes to undergo such treatment.

Despite the currently available treatment options, around 60% of newly diagnosed adult AML patients who are 60 years of age or younger and 90% of patients who are older than 60 years of age are not cured. Outcome in the heterogeneous group of R/R AML patients is relevantly worse. In conclusion, although not approved, treatment options with relevant clinical activity are available in the EU. Therefore, enasidenib needs to show a major therapeutic advantage over these existing therapies in the context of CMA.

6.1.3. Main clinical studies

The efficacy claims of enasidenib in IDH2 mutant R/R AML patients are based on the single pivotal study AG221-C-001. Study AG221-C-001 is an uncontrolled, open-label, multicentre first-in-human phase 1/2 study in subjects who have advanced haematologic malignancies with an IDH2 mutation, including R/R AML (non-curative setting). The analysis population discussed in this MAA – being a subpopulation of the study population – was a high-risk R/R AML population in a non-curative setting. Main efficacy endpoints were CR rate, CR+CRi/CRp rate, ORR, duration of response and OS. Sample size considerations were based on safety (part 1) and the aim to provide evidence for clinically significant activity by excluding CR rate of ≤15% and ORR of ≤25%, respectively (part 2). However, confirmatory hypothesis testing was neither planned nor performed but only descriptive analyses were provided.

To assess the benefit and value of enasidenib in the context of existing therapies used in the R/R AML population, the Applicant performed

- a systematic review of published literature and
- a comparison of the AG221-C-001 data versus AML registry data collected in R/R AML patients with an IDH2 mutation treated with conventional treatments in a real-world setting (the mentioned registries being the AMLSG (Germany) and PETHEMA (Spain)).
- A propensity score matching analysis of study AG221-C-001 vs French Chart Review and vs AMLSG

Furthermore, a randomised controlled phase 3 study (AG-221-AML-004) is ongoing.

To further support these results in the proposed indication in the scope of a CMA application, the Applicant proposes confirmation of benefit-risk (overall survival) as a post-authorisation measure with submission of the clinical study report from the ongoing open-label randomised controlled phase 3 study AG-221-AML-004 (IDHENTIFY) comparing enasidenib monotherapy with conventional care regimens in an elderly (≥60 years) late stage (2nd and 3rd relapse) IDH2 mutated R/R AML population (primary endpoint: OS).

6.2. Favourable effects

Study AG221-C-001

A total of 42/214 (19.6%; 95% CI 14.5, 25.6) subjects in the combined Phase 1/2 R/R AML population treated with 100 mg enasidenib daily achieved a best response of CR (investigator assessment). Duration of CR was 7.4 months (95% CI 6.5, 16.3) for the combined phase 1/2 population.

Subjects who achieved CR with enasidenib also had the highest chance to achieve or maintain RBC and/or platelet transfusion independence (TI).

Median OS in the R/R AML population treated with enasidenib 100 mg daily was 8.8 months (95% CI 7.7, 9.6).

A total of 19/214 (8.9%) R/R AML patients were able to electively discontinue enasidenib and to directly proceed to allogeneic HSCT. Most of the 19 subjects achieved a CR or CRi/CRp (n=14; 73.9%) as a result of enasidenib treatment. Median OS from the first dose date of enasidenib was 23.6 months (95% CI: 10.6, NA) and by this was in the same range than for the CR overall R/R AML population receiving enasidenib monotherapy until progression or unacceptable toxicity [22.9 months (95% CI: 13.2, NE); n= 42].

Enasidenib is an orally administered monopharmacotherapy, rendering outpatient pharmacotherapy of the underlying disease in a population with short life expectancy possible.

6.3. Uncertainties and limitations about favourable effects

Study AG221-C-001

The efficacy claims of enasidenib in IDH2 mutant R/R AML patients are based on a single phase I/II pivotal study.

The efficacy claims of enasidenib in IDH2 mutant R/R AML patients are based on an uncontrolled study.

Study and target population are very heterogeneous.

The lack of proper controls of study AG221-C-001 hampers any robust evaluation of clinical benefit in the context of a heterogeneous condition such as AML. In particular, time-to-event endpoints strongly associated with clinical benefit in AML, such as OS, are of difficult interpretation in single-arm studies, mainly because of the numerous factors involved in survival times that can hardly be controlled in the absence of proper randomisation. Further, the uncontrolled design of study AG221-C-001 also prevented the collection of relevant HR-QoL measures that are of significant importance in life-threatening conditions like AML with a strong impact on patient well-being and life-expectancy.

Since initiation, first-in-human study AG221-C-001 was amended 7 times, finally with the aim to use it as pivotal evidence in an MAA. Amendments of this study include modifications of the study population,

posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size (list incomplete).

The population of R/R AML patients being analysed in this MAA is a subpopulation of the overall study population from study AG221-C-001 that generally included patients with advanced haematologic malignancies with an IDH2 mutation (214/345).

Younger subjects (i.e. patients aged < 70 years) benefit less form enasidenib compared to older subjects in terms of ORR, CR and CR+CRi/CRp rates and median OS. Response to enasidenib in this subgroup might be confounded by the increased number of previous chemotherapy lines received. It is also noted, however, that intensive chemotherapy followed by HSCT still represents the only curative option for fit patients in early lines of relapse, so the actual place in therapy of enasidenib in this subpopulation is hardly definable.

EFS, CR rate, CR/CRi/CRp rate and ORR are not considered established or validated surrogate markers for OS in AML.

The clinical relevance of response rates (CR, CR/CRi/CRp and ORR respectively) in the non-curative setting of R/R AML is unclear.

Contribution of treatment to time related endpoints such as OS and EFS cannot be directly ascertained in a single arm study.

A median OS of 8.8 months (95% CI 7.7, 9.6) in the R/R AML population is in the range described to be between 3.3 in an advanced population and 13.1 months in early disease population and reflects the impact of disease heterogeneity in the R/R-AML population. Thus, no further conclusions can currently be drawn from this information.

Although transfusion independence in principle could be a clinically relevant endpoint, the use of this data from study AG221-C-001 as pivotal evidence is seriously hampered by the following reasons:

- The endpoints regarding transfusion independence were added retrospectively in the knowledge of the results
- The Applicant's definition of transfusion (in)dependence ("at least 1 RBC within 8 week period at baseline") is not considered robust. It is referred to the definition applied by the same applicant for lenalidomide in the treatment of MDS, which reads "*RBC-transfusion-dependent anaemia defined as receiving ≥ 2 units of RBCs within 8 weeks of the first day of study treatment. Patients must have received at least 2 transfusions in each of the 8-week periods during the 16-week pre-treatment period and must not have been transfusion free for any 56 consecutive days during the 16-week pre-treatment period.*"
- As no universally agreed definition of transfusion (in)dependence exists, it is notable, that the definition of this endpoint was performed in the knowledge of the study data.
- Transfusions were administered according to clinical evaluation, which could vary according to country and institution policy.
- Transfusion history was only partially collected prospectively

Interestingly, while planning the currently ongoing phase 3 study AG-221-AML-004 the Applicant did not consider the endpoint of transfusion (in)dependency to be of relevant importance. In that study 'haematologic improvement' is not a key secondary, but only one of multiple secondary endpoints and represented as "additional secondary efficacy analyses" in the statistical analysis. 'Transfusion (in)dependence' is not even listed as an endpoint in study AG-221-AML-004.

Analyses to support the clinical benefit, such as, e.g., rates of infection, bleeding, and neutropenia during response periods are regarded as clinically relevant, but results are of limited value because of

the potential for bias and the lack of a control making it impossible to establish the size of effect attributable to treatment in the frame of an uncontrolled trial.

The Applicant performed a post-hoc analysis of the difference seen in OS between phase 1 and phase 2 [phase1: 9.9 (8.3, 11.6); phase 2: 7.0 (4.9, 8.8)]. Although an imbalance in baseline characteristics of poor prognostic factors disfavouring patients in phase 2 and differences in the access to subsequent treatments appear to explain the difference at least partly, the hazard of death was still numerically increased for phase 2 patients after adjustment for baseline covariates, further highlighting the importance of known and unknown prognostic factors in survival evaluations in AML and the difficulties in performing indirect OS comparisons in the absence of proper randomisation.

Enasidenib might still represent a valuable option as bridging therapy to HSCT, due to its limited myelotoxicity, yet only 19 patients received HSCT following treatment with enasidenib, and few details were provided on post-transplant disease-control rates and on the safety profile of HSCT following enasidenib. In addition, no information on the rate of molecular CR and flow cytometry/cytogenetic-confirmed CR with enasidenib was provided. This is of clinical relevance, since pre-transplant depth of remission has a significant impact on post-transplant outcomes and might drive treatment choice in the "curative" setting.

Subjects with ECOG ≥2, CNS involvement and recent HSCT were excluded from trial participation, and no information on the efficacy of enasidenib in these clinically relevant populations is available.

Severe chemoresistance is not unusual in heavily pre-treated patients, and these limited data suggest that mIDH2 inhibition alone might not be sufficient to overcome the negative impact of prior treatments.

The evaluation of treatment benefit based on presented data from external controls (i.e. literature review, registry data and propensity score matching, details see above) is hampered by the well-known difficulties to establish comparability of treatment group and external control group. In particular, although propensity score matching reduces differences regarding the matching covariates, these represent only a small subset from the known prognostic factors and additional factors may still be unknown. A relevant selection bias cannot be excluded.

The pharmacodynamic data currently presented are inconclusive with regard to observed differences between R140 and R172 mutant IDH2. No consistent correlations could be established as plasma levels do not correlate with 2-HG reduction, 2-HG reduction does not correlate with response, and plasma levels do not correlate with response.

Median OS in subgroups defined by quartiles of baseline mIDH2 VAF (both mutants together) was significantly different between highest and lowest quartile with median 10.66 vs. 5.16 months (Q4 *vs.* Q1: HR 2.45 [1.30, 4.63].

Currently, no clinical study data are available on the impact of potential enasidenib-resistant IDH2 variants on clinical outcomes, in view of recently published data of acquired secondary-resistance mutations in R140Q-mIDH2 patients (Intlekofer et al., Nature, 2018). It seems, however, that treatment-relapse is less likely related to the mIDH2 enzymes, but due to growth of concurrently co-mutated untargeted clones.

Due to the putative mechanism of action, MRD negativity is uncommon with enasidenib and mIDH2 VAF positivity is retained in mature GM cells, although definitive conclusions are hampered by limited sample size, underlining that this targeted treatment with enasidenib alone is not sufficient for a durable clinical benefit in the target population.

6.4. Unfavourable effects

The TEAEs of enasidenib related (IDH) differentiation syndrome, leukocytosis and tumour lysis syndrome as well as gastrointestinal disorders and hyperbilirubimemia were determined as ADRs associated with the mechanism of action of enasidenib:

Treatment-emergent AEs of IDH differentiation syndrome (i.e. rapid weight gain, pleural and pericardial effusions, peripheral oedema, respiratory distress, and fever) were reported in 39 (11.3%) subjects and, with the exception of 1 case, all were attributed to the study drug treatment. Treatment emergent AEs Grade 3-4 were reported in 22 (6.4%) patients. In addition, IDH differentiation syndrome was considered a TESAE for 25 (7.2%) subjects. The first episode occurred mostly within the first 3 months on treatment and it can be accompanied by leukocytosis and TLS. No reliable predictor for IDH DS was identified, although a possible trend towards a higher risk for subjects with >30% bone marrow blasts at baseline was observed.

Treatment-emergent AEs of leukocytosis (all grades) were reported in 53 (15.4%) subjects. 4.6% of TEAs were considered treatment related. Treatment-emergent AEs Grade 3-4 were reported in 19 (5.5%) subjects. 1.7% of TEAs were considered to be treatment related. In addition, non-infectious leukocytosis was considered a TESAE for 22 (6.4%) subjects; for 8 (2.3%) subjects, the TESAE of non-infectious leukocytosis was considered related to study treatment.

27 (7.8%) subjects had a TEAE (all grades) of tumour lysis syndrome. Thirteen (3.8%) subjects had tumour lysis syndrome that was considered by the investigator to be treatment related. Treatment-emergent AEs Grade 3-4 were reported in 19 (5.5%) subjects. 1.7% of TEAs was considered treatment related. Tumour lysis syndrome was considered a TESAE for 21 (6.1%) subjects.

Treatment-emergent AEs in the SOC gastrointestinal disorder were reported for 88.1% of subjects overall, and approximately half of the events (43.8%) were considered by the investigator to be treatment related. Gastrointestinal disorder TESAEs were reported for 22.3% of subjects.

Blood bilirubin increased was reported in 117 (33.9%) subjects, hyperbilirubinemia in 31 (9.0%) subjects, jaundice in 5 (1.4%) subjects, and bilirubin conjugated increased in 3 (0.9%) subjects. Most of these TEAEs within the biliary SMQ were assessed as related to study drug by the investigators (86.3%; 120/139). Treatment-emergent AEs Grade 3-4 were reported in 49 (14.2%) subjects. 10.4% of these TEAs were considered treatment related. There were 121 (35.1%) on-treatment all-cause deaths. Most of these events of death were caused by disease progression or TEAEs related to the underlying malignancies.

6.5. Uncertainties and limitations about unfavourable effects

The uncontrolled design of pivotal study AG221-C-001 limits robust evaluation of enasidenib safety profile. To overcome this limitation, the Applicant submitted the results from indirect comparison exercises, yet similar inclusion/exclusion criteria are not considered sufficient to account for all the possible variables with a potential significant impact on safety in AML. Only data from proper randomization in the context of well controlled trials can adequately inform B/R evaluations in a regulatory context.

The actual incidence of enasidenib related differentiation syndrome (DS), non-infectious leucocytosis (NIL), tumour lysis syndrome (TLS) and gastrointestinal disorders with enasidenib is hard to establish without proper controls, due to frequent overlapping with other clinical manifestations of AML, or with persisting toxicity from previous treatments.

The risk of the observed TEAE of enasidenib related (IDH) differentiation syndrome is new and seems to be quite specific to IDH-inhibitors. Thus, there is a need to further characterize this risk (e.g. identify subgroups at particular risk better characterise frequency in a larger population, specify time to onset and effectiveness of precautionary and protective measures).

Long-term safety data is limited. Only 48/214 patients in the R/R AML Enasidenib 100 mg population respectively 92/345 patients in the total population have been exposed to enasidenib for >12 months. No separate analysis on the safety in these patients has been provided till now.

Clinically relevant safety data regarding hepatic impairment as well as drug-drug interactions is currently missing.

6.6. Effects Table

Effects Table for enasidenib in AML (study AG221-C-001; data cut-off: 01 Sep 2017).

Effect	Short Description	Unit	Enasidenib	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
CR	Complete Remission rate	%	19.6 (14.5, 25.6)	NA	the clinical relevance of CR in AML especially in the non-curative setting is unclear lack of control in a very heterogeneous population	See "clinical efficacy section"
DoCR	Duration of CR	months	7.4 (6.5, 16.3)	NA	the clinical relevance of DoCR in AML is unclear lack of control in a very heterogeneous population	
OS	Median time from randomisation until death by any cause	months	8.8 (7.7, 9.6)	NA	time related endpoints cannot be directly ascertained in an uncontrolled study	
Unfavourable Effects						
Effect	**Short Description**	**Unit**	**Enasi-denib**	**Control**	**Uncertainties/ Strength of evidence**	**References**
IDH Differentiation syndrome	rapid weight gain, pleural and pericardial effusions, peripheral edema, respiratory distress, and fever	% of patients	11.3 % Nearly all events were considered related	NA	Relationship to treatment plausible Lack of control in a very heterogeneous population	See "clinical safety section"

Effect	Short Description	Unit	Enasidenib	Control	Uncertainties/ Strength of evidence	References
Non-infectious leukocytosis	Increase of WBC	% of patients	15.4% 4.5% of events were considered related	NA		
Tumour lysis syndrome	caused by breakdown of WBC infiltrates in the peripheral tissue	% of patients	7.8 % 3.8 % of events were considered related	NA		
Blood bilirubin increased		% of patients	33.9 % Most of the events were considered related	NA		
Gastro-intestinal disorder	Nausea, vomiting, diarrhea and abdominal pain	% of patients	88.1 % 43.8 %of events were considered related	NA		

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Favourable effects

Study AG221-C-001, which is the single pivotal study supporting the application, is an uncontrolled, open-label phase 1/2 study. The analysis population discussed in this MAA – being a subpopulation of the study population – was a high-risk R/R AML population in a non-curative setting.

Due to limited life expectancy, overall survival (OS) represents the best endpoint to inform benefit/risk evaluation in the target population. The impact of treatment on OS, however, cannot be disentangled from prognostic factors. Therefore, a treatment effect on OS can be established only in comparison to an adequate control, which has to be an external control group for single arm trials. However, it is in general almost impossible to establish the comparability of a treatment group and an external control group. This applies in particular in this case where the underlying disease is very heterogeneous with many known prognostic factors influencing OS [e.g. age at relapse, relapsed or refractory disease, nature of AML (de novo vs secondary), cytogenetics, relapse-free interval from first CR, number of prior therapies, prior HSCT, the performance status of the patients, therapy after failure of enasidenib (list incomplete)]. Furthermore, the existence of additional yet unknown prognostic factors influencing survival cannot be excluded. Therefore, the inability to control bias is the major and well-recognized limitation of comparisons to external controls, making these approaches unsuitable as main source of evidence to draw B/R conclusions. Thus, OS results from the proposed pivotal SAT AG221-C-001 must remain descriptive and non-inferential.

In contrast, CR only occurs rarely in the absence of active treatment. Therefore, all CR seen in a SAT can be ascribed to the test agent (whereby CR needs to be evaluated in conjunction with DoR). Relevant activity in terms of response and DoR is a necessary condition for clinically relevant benefit, i.e. an effect on hard clinical endpoints such as OS can be expected only if a relevant activity is observed. Consequently, CR (+ DoR) must be the basis for the inference of a potential clinical benefit from the presented pivotal SAT. However, in the context of indirect comparisons, the results in terms of CR and DoR must be outstanding in relation to what can be achieved with existing therapeutic options in order to be sufficiently confident that the activity of the new compound is clearly superior to the existing therapeutic options. Furthermore, it is noted, that CR is not an established surrogate endpoint for OS in AML, therefore, even if an outstanding effect on CR is observed, the assumption that this translates into an effect on OS should still to be supported by a comparison of OS to external controls (acknowledging the limitations of such a comparison discussed above).

In this specific case of SAT AG221-C-001 the reported CR (19.6%, 95% CI (14.5, 25.6)) and DoR (7.4 months) observed suggest promising clinical activity of enasidenib monotherapy in the studied population. However, these results are far below what could be considered 'outstanding' in relation to available therapies, thus the most important condition for acceptance of study AG221-C-001 to provide evidence for relevant efficacy is not fulfilled. The applicant was given the opportunity to further justify clinical benefit in the target population. In the response, the applicant tried to provide additional justification of clinical benefit by providing results of additional comparisons of OS in study AG221-C-001 vs external controls. However, as discussed above, the comparison of OS to external controls may be considered, at most, as important supportive information, but it cannot establish evidence of clinical benefit in itself, as it cannot be concluded that the observed OS differences are attributable to treatment alone.

Further uncertainties

The pivotal open-label study AG221-C-001 was amended 7 times impacting multiple fundamental aspects of the study design (e.g. study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size). In addition, the population of R/R AML patients being analysed in this MAA is a subpopulation of the overall study population from study AG221-C-001. Summarising these aspects data provided from study AG221-C-001 are exploratory, analyses performed are descriptive.

Regarding the endpoint of transfusion (in)dependency it needs to be concluded that it provides exploratory data of very low level of evidence for the above-mentioned reasons (see "5.3. Uncertainties and limitations about favourable effects"). In consequence, no relevant efficacy claims regarding benefit/risk assessment in an MAA can be derived from this descriptive data.

The prognostic impact of mutated IDH2 in AML remains controversial. Currently it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH2 in AML.

Unfavourable effects

Importance / clinical relevance, strength of the evidence and impact of the uncertainties

The available data suggest that the safety profile of enasidenib is not negligible, as potential life-threatening AEs like IDH differentiation syndrome were identified, yet still manageable in the context of a severe condition like r/r AML. However, the uncontrolled design of the pivotal limits also a robust evaluation of enasidenib safety profile, in particular when the known heterogeneity of AML in terms of disease symptoms, organ involvement and toxicity from prior regimens is taken into account.

The TEAEs of enasidenib- related (IDH) differentiation syndrome, leukocytosis and tumour lysis syndrome as well as gastrointestinal disorders and hyperbilirubimaemia were determined as ADRs

associated with the mechanism of action of enasidenib. Overall these toxicities appear to be manageable.

However, as the risk of the observed TEA of IDH differentiation syndrome is new and seems to be quite specific to IDH-inhibitors there is still a need to further characterize this risk (e.g. identify subgroups at particular risk better characterise frequency in a larger population, specify time to onset and effectiveness of precautionary and protective measures). In addition, further information (from trial AG221-C-004) is needed regarding myelosuppression.

6.7.2. Balance of benefits and risks

Given the poor prognosis of patients with R/R AML, the treatment effect of orally administered enasidenib monotherapy is in principle considered clinically interesting and the safety profile appears manageable. However, it is still not possible to conclude that clinical benefit has been established based on the evidence presented. CR and DoR results from single arm trial (SAT) AG221-C-001 in a very heterogeneous population are not considered outstanding in relation to available therapies. Due to the limitations of comparisons to external controls, OS results from SAT AG221-C-001 remain descriptive and non-inferential. In particular, comparability of the AG221-C-001 treatment group with external control group(s) based on the presented matching methods is still not considered to be established, making it impossible to conclude that the observed OS differences are attributable to treatment.

Regarding the wording of the indication still a formal MO exists. However, it is highlighted that it is a subordinated MO requiring that the benefit/risk balance can be confirmed as positive, which is currently not foreseeable.

6.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease, and is designated as an orphan medicinal product.

As a post-approval commitment to provide confirmatory data in the proposed CMA framework, the Applicant is proposing to submit the results from an ongoing Phase III trial (AG221-AML-004) comparing enasidenib vs. conventional care regimens in older subjects with late stage mIDH2+ r/r AML.

The study design of confirmatory trial AG221-AML-004 has been agreed in the context of a SAWP/CHMP SA procedure and is considered adequate to support clinical benefit evaluations in the studied population.

6.8. Conclusions

The benefit-risk balance of enasidenib is considered negative. Major objections exist regarding the lack of sufficient evidence of efficacy and formally regarding the indication wording.